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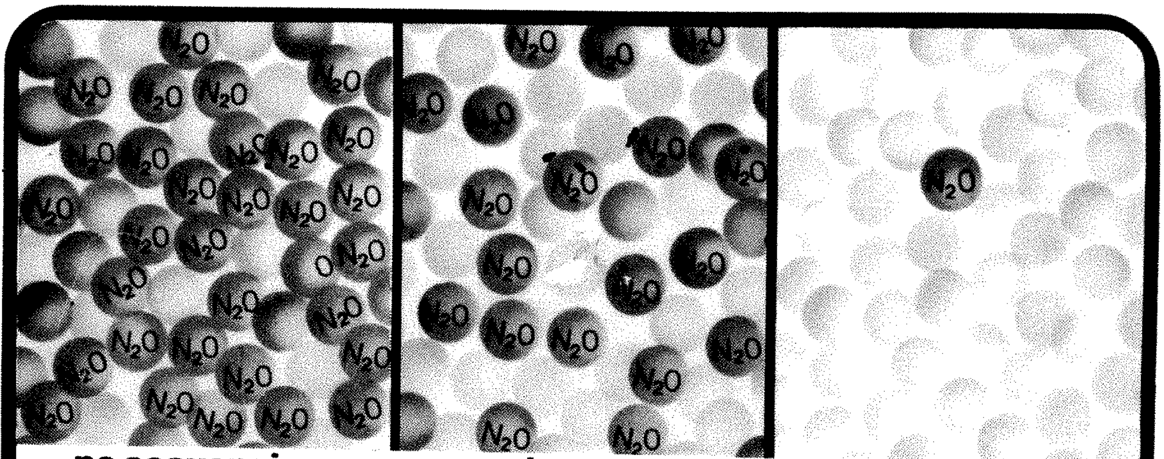

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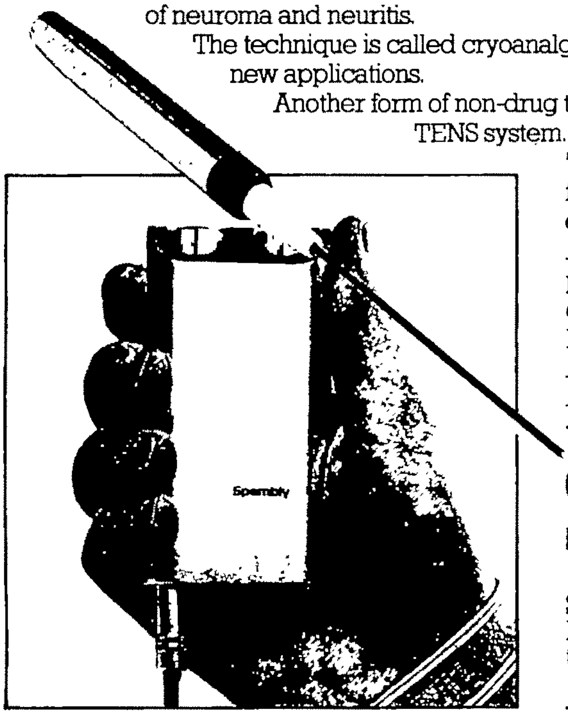

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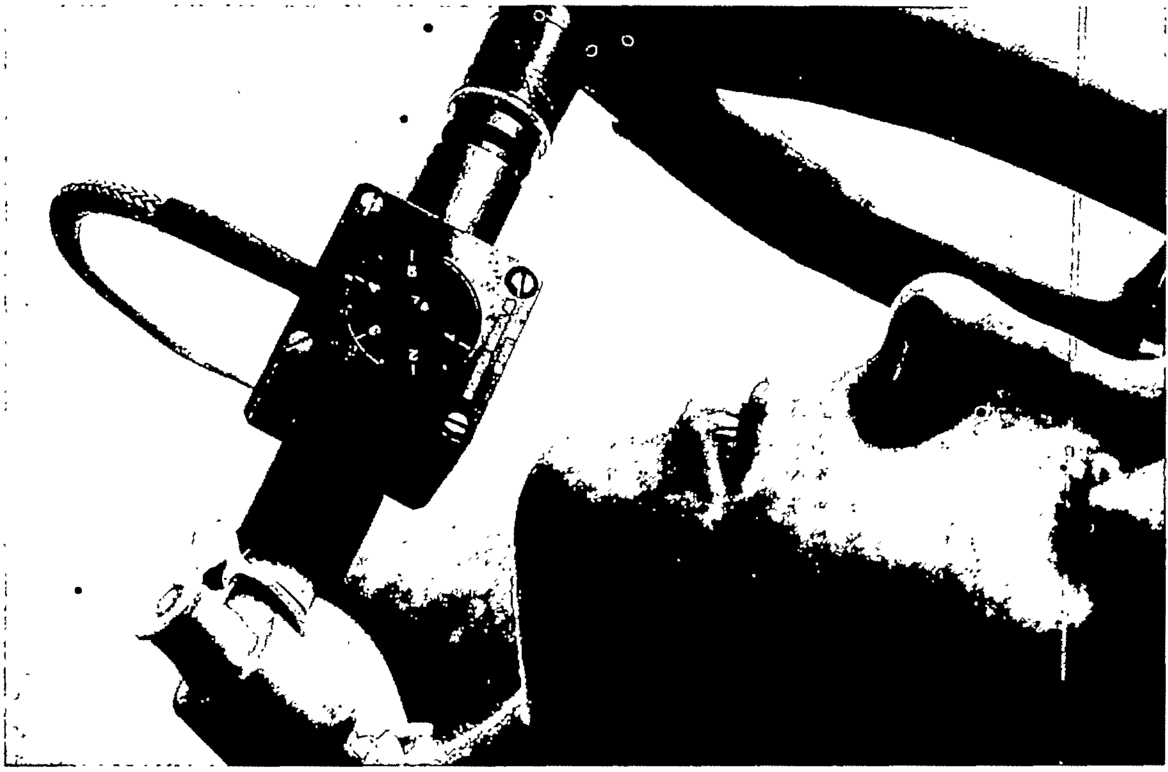

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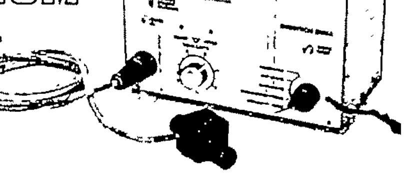

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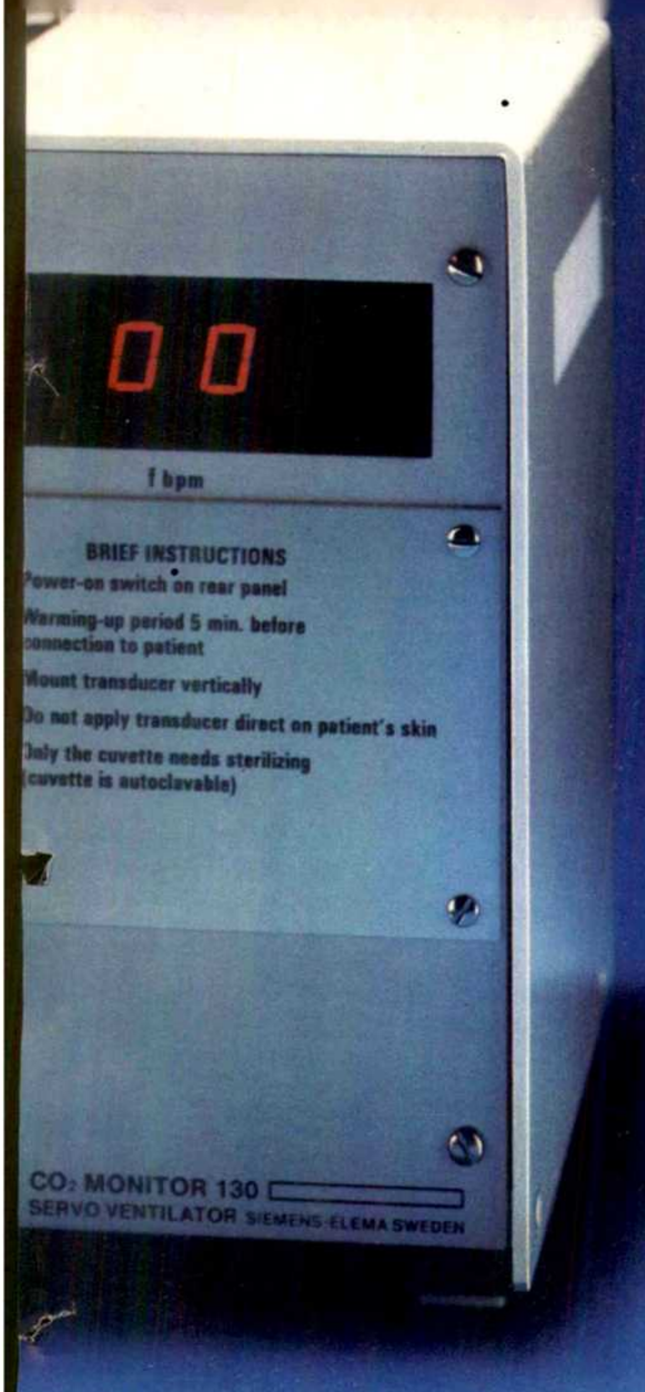
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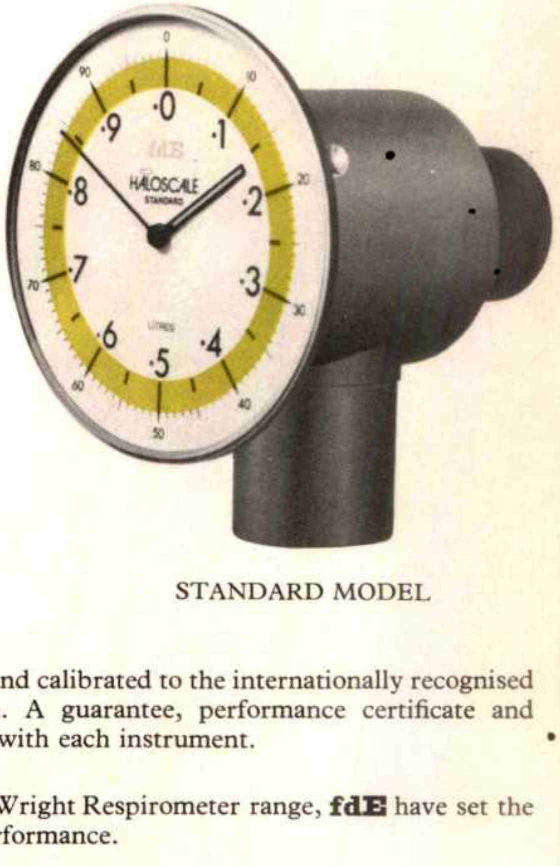

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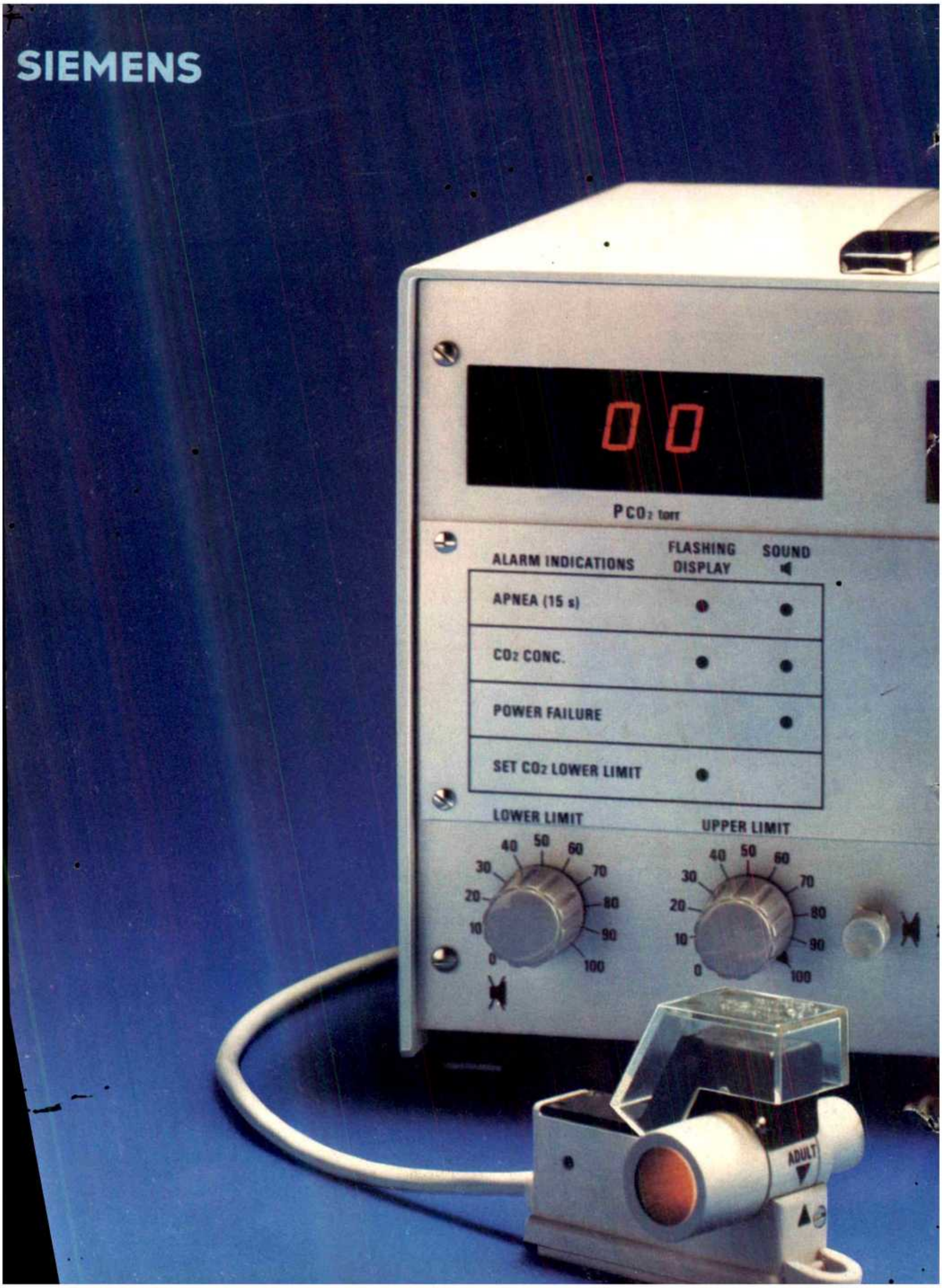
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1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

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Minor side-effects may include a transient flush an muscle twitching, the latter occurring more often i patients given hyoscine alone as premedication. There is a possibility of generalised convulsions, a of cardiac arrhythmias in patients concomitantly treated with muscle relaxants. Short periods of coughing, hiccoughing, salivation, laryngospasm c shivering may occur, particularly in association wi light anaesthesia or rapid injection.

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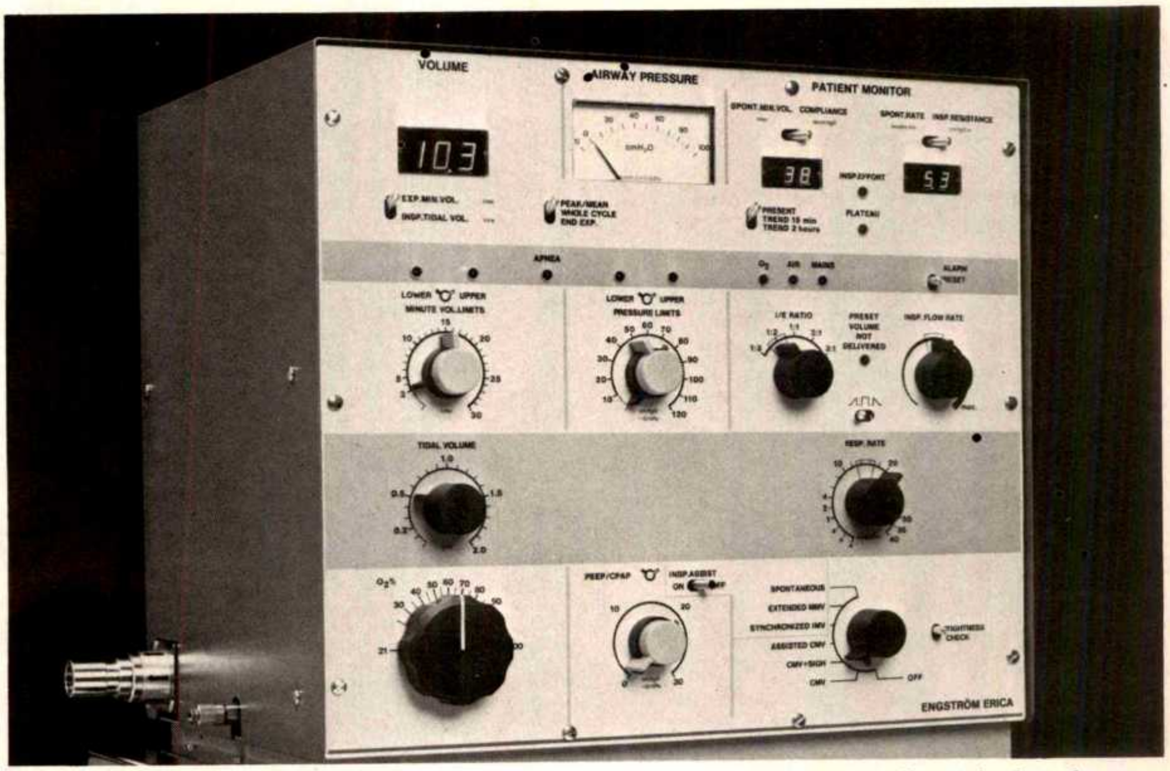

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 53, No. 7 JULY 1981

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EDITORIAL

VASCULAR DISEASE AND ANAESTHESIA

Cardiovascular disease, in particular the atheromatous process, has become the hallmark of, and the predominant cause of death in, affluent, overfed, underexercised societies. Atheromatous disease, hypertension and the effects of ageing of the arteries can all exist singly or together, so that a high proportion of patients over the age of 40 years presenting for anaesthesia and surgery are more at risk from the effects of these conditions than their normal counterpart. This issue is devoted to consideration of the problems of anaesthesia for patients with arterial disease. Pathophysiology, medical assessment and treatment, and advances in diagnosis and monitoring are considered together with the clinical management of patients with cerebrovascular and coronary arterial disease.

Involvement of the coronary arterial system by the atheromatous process creates the pattern of ischaemic heart disease which is the single most important medical condition which places the patient presenting for anaesthesia at increased risk of perioperative morbidity and mortality. The insidious progress of the atheromatous process is consistent with a normal life pattern free of symptoms until the first appearance of angina, or the catastrophic effects of a myocardial infarct. Thus most of the patients at risk during anaesthesia because of coronary arterial disease present neither history nor symptoms to aid the detection of their condition at assessment before operation. Less than a quarter present with a clear history of angina or of a previous myocardial infarct. There are still insufficient epidemiological studies which accurately identify the risk factors for these patients, and which document the nature and results of morbid events occurring during the perioperative period.

High arterial pressure is not a normal manifestation of coronary artery disease, but where it exists independently it aggravates and accelerates the course of the atheromatous process. Systolic hypertension (> 200 mm Hg) without concomitant diastolic hypertension (< 90 mm Hg) is a common finding in patients with generalized arteriopathy, and represents a state of increased cardiac output into a rigid vascular system. Patients with this response behave very differently from the patients with diastolic hypertension (> 100 mm Hg), the hallmark of renal, endocrine or primary (essential) hypertension. It is equally important to recognize the rigid arteriopath at the assessment before operation because even if the systolic pressure is very high (> 200 mm Hg), no benefit will be achieved by postponing surgery. By contrast, the patient with untreated severe diastolic hypertension (> 110 mm Hg) may well benefit from postponement and medical antihypertensive control. The major causes of perioperative morbidity for the hypertensive patient are coronary and cerebrovascular ischaemia. The former may be secondary to combined hypertension and tachycardia as a result of reflex autonomic responses to noxious stimuli, or when moderate diastolic hypotension decreases coronary perfusion. Cerebrovascular accidents may occur during anaesthesia when the hypertensive patient subjected to undue arterial hypotension develops an ischaemic lesion, or in the period after surgery when severe uncontrolled hypertension may cause an intracerebral haemorrhage.

Improved management of the patient with severe vascular disease depends on progress in the understanding of the pathophysiological basis of the disease process and in the management and assessment of the patient before operation, and not least the application of new and improved monitoring techniques to detect their unpredictable haemodynamic vargaries.

C. Prys-Roberts

Br. J. Anaesth. (1981), **53**, 675

THE PATHOLOGY OF ARTERIAL DISEASE

A. G. MACIVER AND P. J. GALLAGHER

Cardiovascular disorders are now the leading cause of death in most Western societies. In England and Wales ischaemic heart disease currently accounts for 27%, and cerebrovascular disorders for 13%, of all deaths (Office of Population Censuses and Surveys, 1980). In clinical practice atherosclerosis is the commonest and most important arterial disease, but many other vascular disorders are recognized. Table I classifies the types of arterial disease.

TABLE I. *Classification of arterial disease*

(1) Age-related changes (arteriosclerosis)
(2) Atherosclerosis
(3) Hypertensive
(4) Diabetic
(5) Immune complex vasculitis
    Systemic lupus erythematosus
    Rheumatoid vasculitis
    Polyarteritis nodosa
    Henoch–Schönlein Syndrome
    Subacute infective endocarditis
    Wegener's granulomatosis
(6) Diseases of uncertain aetiology
    Giant cell arteritis
    Scleroderma (systemic sclerosis)
    Buerger's disease

NORMAL ARTERIAL STRUCTURE

In all areas of the arterial system three anatomical layers can be distinguished. The innermost, the intima, is composed of a single layer of endothelium with a thin supporting framework of connective tissue. The internal elastic lamina (fig. 1) separates the intima from the media. The aortic media is rich in elastic tissue, but in the majority of medium sized arteries, such as the coronaries, smooth muscle predominates. The outermost layer, the adventitia, is connective tissue. Small blood vessels, the vasa vasorum, enter the media from the adventitial aspect and supply much of the media. The intima and the inner media survive by direct diffusion from the vascular lumen.

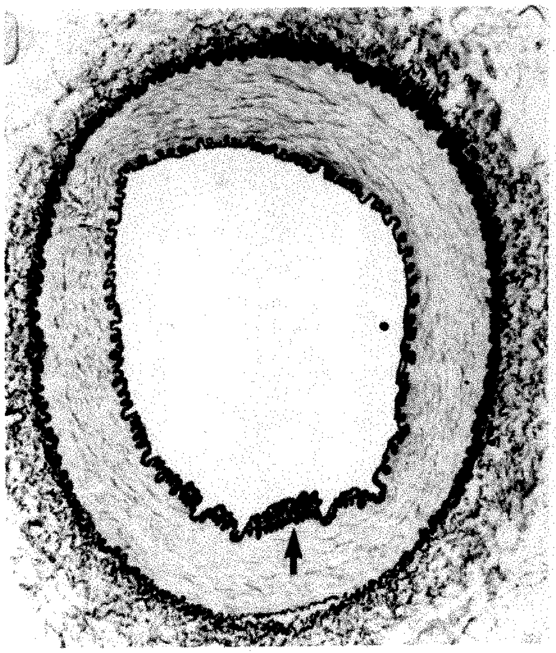

FIG. 1. A normal small muscular artery (male, aged 19 yr). The only abnormality is a small area of reduplication of the internal elastic lamella (arrow). Elastic–Van Gieson. ×65.

AGE-RELATED VASCULAR CHANGES

Significant vascular abnormalities occur in normotensive elderly subjects. Although there is considerable individual variation, changes are rare before 40 and most common after 70 years. The major alterations are in connective tissue. Collagen turnover decreases with age and there are changes both in amino acid composition and the degree of cross-linking between individual fibrils (Prokop et al., 1979). The recoilability of elastin is impaired and there is excessive accumulation of mucopolysaccharide ground substance.

In the aorta the net effect of these changes is to reduce both the strength and elasticity of the wall. Progressive dilatation is a common ageing phenomenon (Mitchell and Adams, 1977). In the ascending aorta this can lead to stretching of the aortic valve ring and aortic incompetence.

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Dilatation is often pronounced in the lower abdominal segment and, in combination with atherosclerosis, produces aneurysms.

Age-related changes in muscular arteries are often termed arteriosclerosis. Even arterioles, vessels with an outside diameter of less than 100 µm, can be affected. Characteristic alterations include smooth muscle hypertrophy and reduplication of the internal elastic lamella (fig. 2) by the formation of several extra layers of collagen. Intimal fibrosis and thickening of the basement membrane synthesized by the endothelial cells serve to reduce further the diameter of the vessel. However, this reduction is seldom as marked as in hypertensive disease (Davidson, Talner and Down, 1969).

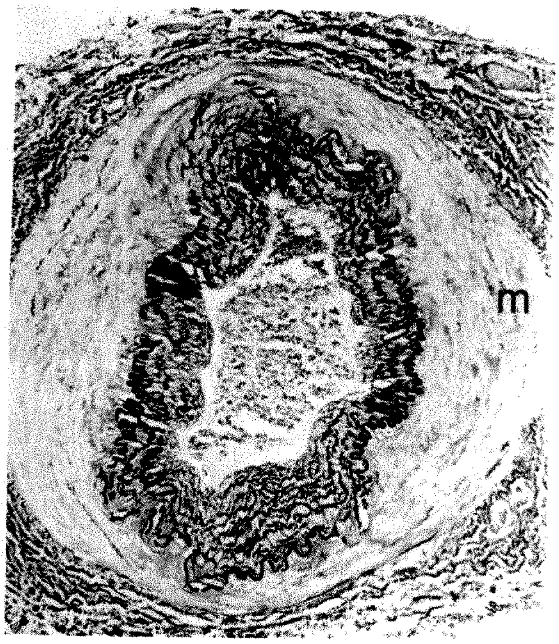

FIG. 2. Ageing changes in the temporal artery of a 68-yr-old female. Numerous layers of newly formed collagen have produced concentric intimal thickening. In this case the media (m) shows no significant changes. Elastic–Van Gieson. × 110.

All parts of the arterial tree can be affected by arteriosclerosis, but the changes have been most extensively studied in the kidney. However, it is far from certain that all ageing changes in the kidney are the result of vascular insufficiency (McLachlan, 1978; Darmady and MacIver, 1980). Although little is known of the aetiology of age-related vascular disease, there is no doubt that arteriosclerosis is an important cause of morbidity, contributing to the high frequency of cardiac, cerebral, colonic and renal ischaemia in the geriatric population. The clinical effects become most apparent when the cardiovascular system is stressed by haemorrhage, major surgery, infection or shock.

ATHEROSCLEROSIS

Although atherosclerosis has been recognized as a distinct disease process for several centuries, there is little doubt that its frequency has increased dramatically over the past 50 years. Large and medium sized arteries are primarily affected and a wide range of clinical disorders results (table II).

TABLE II. *Clinical effects of atherosclerosis in different anatomical sites*

Site of disease	Clinical effect
Aorta, especially abdominal aorta	Atherosclerotic aneurysm Embolism of atherosclerotic debris
Aorto–iliac and femoral system	Intermittent claudication Gangrene
Coronary arteries	Myocardial infarction Angina
Carotid and cerebral arteries	Cerebral thrombosis Transient ischaemic attacks following atheromatous embolism
Renal arterial orifices	Renal ischaemia Hypertension
Mesenteric arteries	Intestinal ischaemia

There are several different types of early lesion (Haust, 1971), but the advanced fibrolipid plaque is the only type of deposit of clinical importance (fig. 3). Progressive enlargement of these lesions can virtually obstruct the lumen of vessels, but

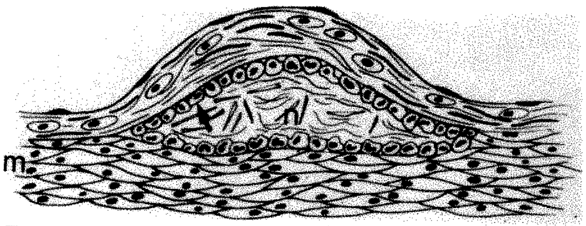

FIG. 3. A diagrammatic representation of an atheromatous plaque. There is a central area of necrosis (n) surrounded by macrophages (arrow). Haemorrhage in this area is responsible for the crystalline deposits of cholesterol. The overlying fibrous cap is largely collagen (thin lines), but also contains a little elastin (thicker lines). In due course the necrotic area will enlarge and further erode the smooth muscle layer (m).

important additional complications are haemorrhage into the plaque and thrombus formation (fig. 4). Rupture of the endothelial covering with exposure of underlying collagen may well be the stimulus to thrombus formation, besides permitting seepage or massive loss of blood from the lumen into the plaque itself. The importance of haemorrhage and thrombus formation as complications of atherosclerosis cannot be overemphasized. For example, coronary arteriography performed within 4 h of acute myocardial infarction has demonstrated total coronary arterial occlusion in more than 80% of cases (De Wood et al., 1980). Furthermore, careful dissection of the coronary arteries in patients dying with established myocardial infarcts reveals coronary arterial thrombi in the vast majority of cases (Davies, Woolf and Robertson, 1976).

Very little is known of the mechanisms which influence where and when plaques develop. Lesions often occur close to arterial bifurcations and haemodynamic factors are clearly of major importance (Stehbens, 1975). Nevertheless, one of the most striking features of atherosclerosis is the wide variation in the distribution of lesions between individuals, even in the same population group.

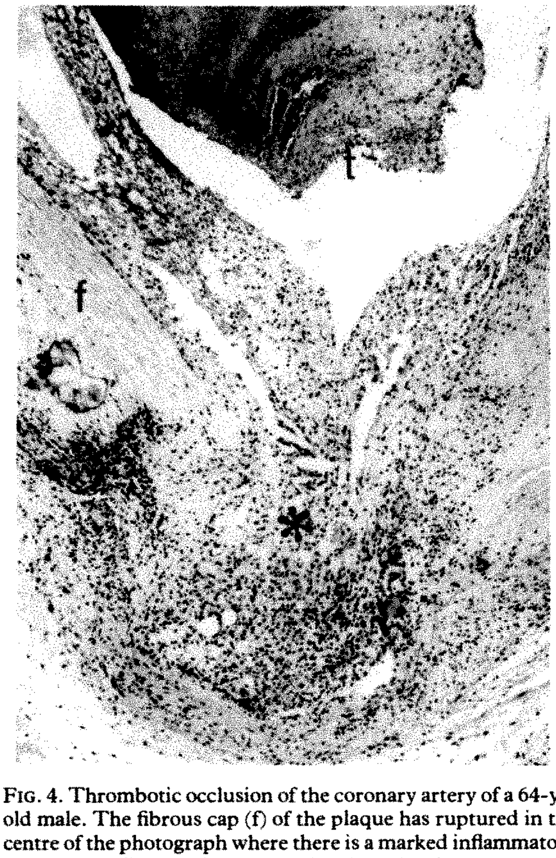

FIG. 4. Thrombotic occlusion of the coronary artery of a 64-yr-old male. The fibrous cap (f) of the plaque has ruptured in the centre of the photograph where there is a marked inflammatory response (*). Part of a large occlusive thrombus is present at the top of the photograph (t). A small area of calcification is arrowed. Haematoxylin and eosin. × 90.

It now seems unlikely that true atheromatous plaques develop from the fatty streaks so commonly seen in the aorta and coronary arteries of young people (Velican and Velican, 1980). Equally, the relationship between atherosclerosis and the age-related changes described above is uncertain.

Aetiology of atherosclerosis

Pathologists have argued for more than a century about the cause of atheroma. Although the wide range of accepted risk factors (table III) suggests a multifactorial aetiology, most attention has focused on the role of dietary lipid and serum lipoproteins and of endothelial injury and subsequent thrombosis (table IV). The earliest lesion is assumed to be an area of endothelial damage or ulceration. Experiments in animals suggest that endothelial injury may be a natural wear-and-tear phenomenon and is accelerated when blood flow is turbulent (Reidy and Bowyer, 1977) or animals are exposed to carbon monoxide (Astrup, 1972) or tobacco smoke (Woolf, 1978).

TABLE III. *Risk factors in atherosclerosis*

Increasing age
Hypertension
Diabetes
Cigarette smoking
Blood lipid abnormalities
  High LDL cholesterol
  Low HDL cholesterol
  ? Hypertriglyceridaemia
? Obesity
? Sedentary life style

Endothelial injury is rapidly followed by platelet aggregation and thrombus formation (Davies et al., 1975). If the original injury is repeated, or becomes persistent, further cycles of endothelial necrosis, thrombus formation and repair inevitably lead to intimal thickening (Ross and Glomset, 1976).

Paradoxically it is smooth muscle cells derived from the arterial media, rather than fibroblasts, which produce the connective tissue of atheromatous lesions (Haust, More and Movat, 1960;

TABLE IV. *The pathogenesis of atherosclerosis*

(A) Evidence for the lipid hypothesis
- Good correlation between increasing concentrations of blood lipids, especially LDL cholesterol, and frequency of atherosclerotic vascular disease.
- Atherosclerotic plaques accumulate more cholesterol and cholesterol esters than adjacent disease-free vessel wall.
- Atherosclerosis can be induced in many animal species by cholesterol or lipid rich diets.

(B) Evidence that endothelial injury and thrombosis play important roles
- Fibrin and platelets can be detected in early lesions.
- Plaques form near arterial branches where haemodynamic flow is most turbulent.
- Experimental damage to the arterial intima is followed by thrombus formation. Persistent injury produces large thrombotic lesions somewhat similar to atheromatous plaques.

(C) Other concepts
- Reduced production of prostacyclin by diseased arterial wall may lead to a relative excess of thromboxane, and subsequent tendency to vascular thrombosis.
- Atheromatous lesions arise from the proliferation of a single clone of arterial smooth muscle cells, perhaps under the influence of a mutagen.

Ross, 1971). Tissue culture experiments have shown that factors derived from platelets, the serum of diabetic or uraemic patients and the low density lipoprotein component of plasma are potent stimulators of smooth muscle cell proliferation (Rutherford and Ross, 1976; Wissler, 1979). It may well be that, *in vivo*, such factors are responsible for the inexorable growth which transforms a flat harmless plaque into the large obstructive lesion so liable to complications such as haemorrhage and thrombosis.

Besides fibrous tissue, all atherosclerotic deposits contain some lipid. Biochemical and immunological studies have emphasized that cholesterol esters and low density lipoprotein are markedly increased in atheromatous lesions (Adams, 1973; Smith, 1974). Clearly, the mechanisms responsible for this accumulation are as important as those which produce the initial endothelial injury.

Many different epidemiological studies have demonstrated a close and independent association between an increased plasma cholesterol concentration and a history, or increased likelihood of developing coronary heart disease (Kannel, 1976; Pelkonen et al., 1977).

In the circulation, cholesterol is bound to carrier proteins secreted by the liver and the small intestine. The frequency of atherosclerotic disease is directly proportional to the concentration of cholesterol bound to low-density lipoprotein, but is inversely related to high density lipoprotein cholesterol concentrations (Glueck et al., 1976; Gordon et al., 1977).

Many different tissues can synthesize cholesterol, but significant amounts can be eliminated from the body only via the bile. Two separate enzymes, lecithin acyl transferase (LCAT) and lipoprotein lipase (LPL), are now known to act at the endothelial surface. A complex biochemical cycle involving different structural forms of high-density lipoprotein and LCAT is currently thought to control the transport of cholesterol between the peripheral tissues and the liver (Miller, 1979).

Given that the formation of a platelet thrombus is the initial response to endothelial necrosis, any factors which influence the aggregation of platelets must have particular relevance to the formation of atheromatous lesions. A series of prostaglandins has been identified which have powerful, and in some ways entirely opposite, effects on platelet and vascular physiology (Moncada and Vane, 1978). In blood platelets arachidonic acid is metabolized via prostaglandin endoperoxides to thromboxane A_2 (TXA_2). In contrast, in blood vessels and in the lungs an entirely separate compound, prostacyclin (PGI_2) is produced. TXA_2 is a powerful vasoconstrictor and promotes the aggregation of platelets, whereas PGI_2 has vasodilator properties and inhibits platelet aggregation. It has been suggested that a balance between these two arms of the arachidonic acid metabolic pathway may be an important homeostatic mechanism in thrombosis and that manipulation of this balance towards the production of prostacyclin could be valuable in the management of thrombotic and obliterative vascular disorders.

The observation that prostacyclin generation is reduced in arterial tissues of rabbits fed with cholesterol suggests that prostaglandins might play a role in the aetiology of atheroma (Gryglewski et al., 1978). A vicious cycle can be postulated in which the development of an atheromatous plaque is associated with reduced prostacyclin production. The resultant relative excess of thromboxane A_2 would favour platelet aggregation and thrombus formation, events that can only accelerate the further development of atheromatous lesions.

A rather different view of the proliferative process in atherosclerosis was advanced by Benditt and Benditt (1973). Their studies of glucose-6-phosphate dehydrogenase (G6PD) isoenzyme patterns in postmortem samples of aorta indicated that early atheromatous lesions, like benign neoplasms such as uterine leiomyomas, had developed from a single cell, or a single clone of cells. The concept of atherosclerotic plaques as disordered growth processes raises the question of mutagenicity in atherosclerosis. No definite mutagens have yet been identified, but Benditt (1977) has speculated on the role of cholesterol derivatives, aryl hydrocarbons carried in the blood bound to lipoproteins, and substances related to smoking.

Prevention, regression and treatment of atherosclerosis

Reports of substantially diminished atherosclerosis in severely malnourished concentration camp victims first suggested that atheroma might be a reversible process. Experiments in monkeys have confirmed that arterial disease induced by high fat diets can be reversed when a low fat ration is substituted (Gresham, 1976; Wissler, 1978). However, the major dietary changes that can be inflicted on experimental animals are generally unacceptable to human patients. Reviewing the result of recent trials aimed at the prevention of atherosclerotic disease Lewis (1980) has emphasized that reduction in plasma cholesterol of the order of 20% is necessary to ensure a therapeutic result. Changes of this magnitude have been reported using diets in which animal protein is completely replaced by vegetable preparations such as soya flour (Descovich et al., 1980). On a more practical basis, it is wise to advise patients at risk to reduce the total proportion of energy derived from fat, to increase consumption of fibre, such as bran, and wherever possible replace animal by vegetable protein (Shaper and Marr, 1977; Lewis, 1980).

Man's innate reluctance to alter his dietary habits has led to a search for drugs with a hypocholesterolaemic effect. These can be divided into compounds interfering with bile acid or neutral sterol absorption from the intestine (e.g. cholestyramine) and drugs with a primary action on plasma lipid transport (e.g. clofibrate).

A double-blind trial in three European centres demonstrated that clofibrate reduced both serum cholesterol concentrations and the frequency of non-fatal myocardial infarcts. Inexplicably, the crude mortality rate was significantly greater in clofibrate-treated patients, as was the frequency of gall bladder disease (Report of the Committee of Principal Investigators, 1980). Clofibrate could not therefore be recommended as a lipid-decreasing agent for community-wide use. Cholestyramine can produce reductions in plasma cholesterol concentrations of the order of 25–40% in patients with familial hypercholesterolaemia. However, it is an unpalatable drug and compliance rates in a recent long-term study in children were only 60% (West, Lloyd and Leonard, 1980).

Sulphinpyrazone and aspirin both inhibit platelet prostaglandin synthesis and platelet aggregation. Sulphinpyrazone does appear to prevent sudden cardiac death in the high-risk period shortly after acute myocardial infarction (Anturan Reinfarction Trial Research Group, 1980). Total mortality in the first year after infarction is not significantly reduced by aspirin 300 mg three times a day, although the hospital admission rate is somewhat diminished (Elwood and Sweetnam, 1979).

A further approach is the use of beta-adrenoceptor blocking agents. Results to date are somewhat equivocal, although it would appear that beta blockade is beneficial after infarction in patients aged less than 65 years (Anderson et al., 1979).

Until such time as the exact pathogenesis of atherosclerosis is established, prevention can only be based on the reduction, or elimination, of known risk factors (Joint Working Party, 1976). In the United States, where there has been an undoubted recent reduction in the frequency of fatal coronary heart disease, community-wide awareness of these is probably greater than in Europe. Changes in dietary habits, reduction in smoking, better control of hypertension, improved management of acute myocardial infarction and coronary artery bypass surgery are all felt to have contributed to this phenomenon (Stern, 1979). The frequency of coronary heart disease may have stabilized in the United Kingdom, but as yet there is no evidence of a significant decrease.

ANEURYSMS

An aneurysm is a localized dilatation of part of the vascular system. The very fact that dilatation has occurred implies that the vessel wall has been weakened. The commonest cause of this is progressive destruction of the aortic medial elastic tissue by atheroma (table V).

Atherosclerotic abdominal aortic aneurysms frequently rupture into the retroperitoneal space. The classical clinical triad of hypotension, pain and a pulsatile mass is not always present (McGregor, 1976). The only effective treatment is surgery, although the operative mortality is high. Hypotension before operation is a bad prognostic sign, but there is no one group in which surgery holds no hope of saving life (Butler, Chant and Webster, 1978).

TABLE V. *Clinical effects of aneurysms*

Type of aneurysm	Site	Clinical effects
Atherosclerotic	Lower abdominal aorta and iliac arteries	Pulsatile abdominal mass. Lower limb ischaemia. Rupture, with massive retroperitoneal haemorrhage.
Dissecting	Aorta and major branches	Loss of peripheral pulses (e.g. radials). Haemopericardium. External rupture (retroperitoneal haemorrhage). Re-entry causing "double-barrelled" aorta.
Syphilitic	Ascending and arch aorta	Aortic incompetance. Local pressure effects, such as superior vena caval compression.
Berry	Circle of Willis	Subarachnoid haemorrhage.
Microaneurysms (Charcot–Bouchard)	Intracerebral capillaries	Intracerebral haemorrhage.
Mycotic	Root of aorta (direct extension from aortic valve endocarditis). Any vessel	Rupture, e.g. cerebral haemorrhage.

The underlying pathology of dissecting aneurysms is the age-related degeneration of the mid-portion of the aortic media. If a small intimal tear exposes this area of potential weakness to the systolic force of the aortic stream, blood "dissects" the aortic wall into two layers. Without treatment the mortality rate is 50% in 48 h, and 90% within 1 week. The immediate aim of medical treatment is to contain the propagating haematoma by reducing arterial pressure to less than 130/90 mm Hg (Slater and De Sanctis, 1979). Surgical repair is now feasible in many patients.

In so-called "berry" aneurysms of the circle of Willis, the normal muscular arterial wall is replaced by fibrous tissue. The lesions arise at the site of gaps in the muscle of the media and are commoner in patients with hypertension. The most important complication is subarachnoid haemorrhage. Capillary microaneurysms can be found along the course of arteries such as the lenticulo–striate branch of the middle cerebral. They are widely considered to be the precursors of primary intracranial haemorrhage in hypertensive subjects. Fibrinoid necrosis of the capillary wall (see below) may be a preliminary change. In syphilitic and mycotic aneurysms, inflammation is responsible for the weakening of the vessel wall. Both conditions are now rare.

HYPERTENSIVE DISEASE

Hypertension has been defined as "a disorder in which the basal level of arterial pressure is higher than that expected for the sex, age and race of the person." Smith (1977) has described the normal distribution of arterial pressure in an American population.

Although this definition should help to separate the vascular changes of benign longstanding hypertension from those caused by normal ageing, the distinction is not clear cut. This suggests that some of the vessel abnormalities of the elderly may correlate with arterial pressure even if the subject is within the "normotensive range". Further difficulties arise in the recognition of malignant hypertension. Clinical features such as headache and blurring of vision are unsatisfactory discriminants (Bulpitt, Dollery and Carne, 1976). Papilloedema, fundal haemorrhages and exudates are more useful (Kincaid Smith, McMichael and Murphy, 1958), as is the recognition of a rapid and prolonged increase in diastolic pressure and the detection of fibrinoid change in a biopsy (Heptinstall, 1974; Mandal et al., 1977).

Hypertension accelerates atherosclerosis, but the deposits have the same content and distribution as in normotensive subjects. Another change in longstanding and severe hypertension is thickening of the media of muscular arteries. This is the result of hyperplasia of smooth muscle cells and the deposition of extra layers of collagen close to the internal elastic lamina. Arterioles are also affected in hypertension. Marked intimal thickening produces a slit-like lumen. Surprisingly, the media is often thinner than normal, probably because of ischaemic atrophy of smooth muscle.

Hypertensive intimal thickening is a result of myofibroblasts, collagen, excess basement membrane and large deposits of plasma protein, which are called "hyaline" in benign and "fibrinoid" in malignant hypertension (fig. 5). Although there are no satisfactory correlative studies, the quantity of accumulating protein probably depends on the arterial pressure. Hypertension presumably increases the normal flow of protein into the vessel wall and also the amount of high molecular weight protein, such as fibrinogen, that passes through the junctions between endothelial cells. Very great pressures, as in malignant hypertension, are associated with large protein deposits. In addition to IgM, fibrinogen–fibrin and complement (C3), there may be red blood cells, suggesting structural damage to the endothelium. In contrast to immune complex vasculitis, the type of protein detected in hypertension, whether benign or malignant, is unrelated to any form of immunological reaction.

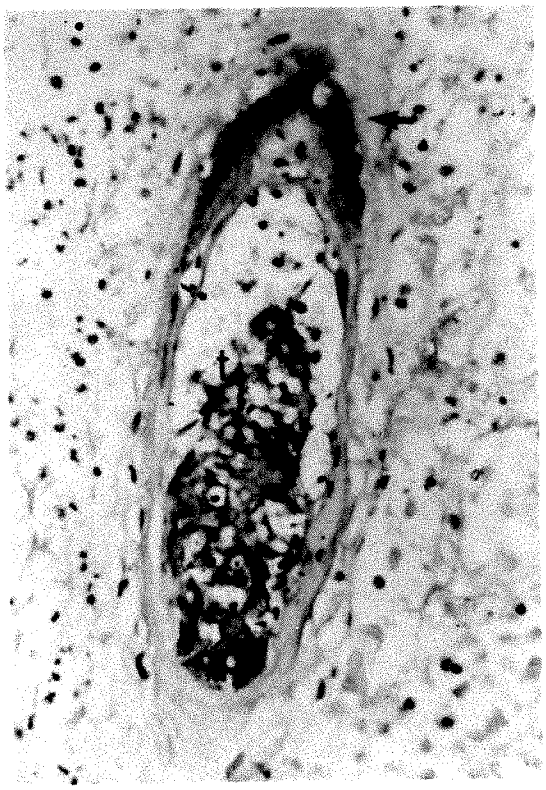

FIG. 5. Arteriole in malignant hypertension. There is fibrinoid change in the wall (arrow) and thrombus in the lumen (t). Haematoxylin and eosin. × 300.

Experimental studies have clearly demonstrated the leakage of carbon and other tracer materials into the subendothelial space of vessels in hypertension (Hüttner, More and Rona, 1970; Goldby and Beilin, 1974). The site of entry is between the endothelial cells in mild hypertension, but through damaged cells in severe hypertension. The cellular component of the thickened intima results from migration of myofibroblasts from the media, through naturally occurring fenestrae or hypertension-induced fractures of the internal elastic lamina. Proliferation and migration occur within 10 weeks of inducing hypertension (Wolinsky, 1972), but the causes are not known.

The effects of hypertension are well-recognized. Major complications occur in cardiovascular, cerebral and renal systems. Atheromatous aortic disease and coronary heart disease with heart failure are frequent. The large hypertrophied left ventricle is particularly at risk from ischaemia, when pressures suddenly decrease in shock or over-enthusiastic hypotensive regimens. Major cerebrovascular accidents result from ruptured congenital aneurysms of the arteries in the circle of Willis and from microaneurysms (Charcot–Bouchard aneurysms) in the cerebral white matter (Pickering, 1970). Diffuse renal ischaemia leads to tubular atrophy with loss of concentrating abilities. This is particularly important in dehydrated elderly surgical patients who already have age-related loss of their loops of Henlé (Darmady, Offer and Woodhouse, 1973). Glomerular damage is not marked at this stage but it occurs later, with eventual renal failure.

DIABETIC VASCULAR DISEASE

Patients with diabetes, particularly juvenile onset insulin dependent diabetes, develop three forms of vascular disease. Atherosclerosis is often severe (Stout and Vallance-Owen, 1969) and predictably involves the aorta and larger arteries.

Hypertensive vascular disease is a frequent complication, especially when there is advanced renal disease.

The most important change is diabetic microangiopathy. The alterations can be found throughout the systemic circulation and can be viewed directly in the retina. Disease of the renal vessels is of particular clinical importance. Arterioles and capillaries are typically affected. The pathology is complex and includes basement membrane thickening (Westberg, 1976), intimal fibrosis and increased vessel wall permeability. The degree of basement membrane thickening is related to the duration and severity of the diabetes, and the adequacy of its control (Williamson and Kilo, 1977). It is not clear if the thickening is the result of increased production or decreased removal of basement membrane. In the kidney, the changes cannot be detected until 18–24 months after the onset of disease.

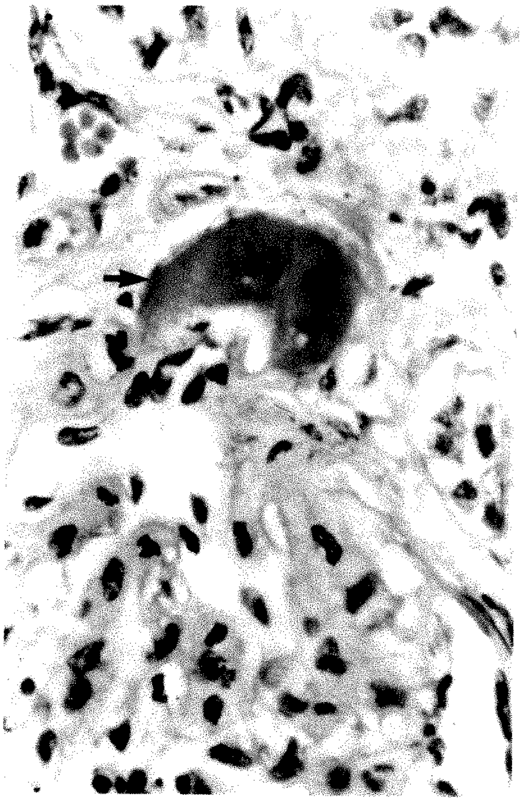

FIG. 6. Diabetic microangiopathy. Arteriole with accumulated protein in the intima (arrowed). Increased basement membrane permeability causes this abnormality. Goldner Trichrome. × 800.

Although thickened, the basement membranes are excessively permeable to plasma proteins. Large subendothelial protein deposits (fibrinoid change, hyaline change) are characteristic (fig. 6). Although the deposits may contain immunoglobulins and complement, there is no evidence that an immunological reaction is involved. It is generally considered that the changes are the result of increased passive transudation of protein from the vessel lumen. At a later stage the basement membrane, which has become progressively thicker, starts to lose permeability, and renal failure supervenes. The intimal thickening of arterioles in diabetes is similar to that seen in ageing and hypertensive vessels (hyaline arteriolosclerosis).

IMMUNE COMPLEX VASCULITIS

It is now recognized that several different vascular disorders have an immunological basis (Theofilopoulos and Dixon, 1980). The essential pathology is deposition of complexes of antigen and antibody in the vessel wall (fig. 7). Immune

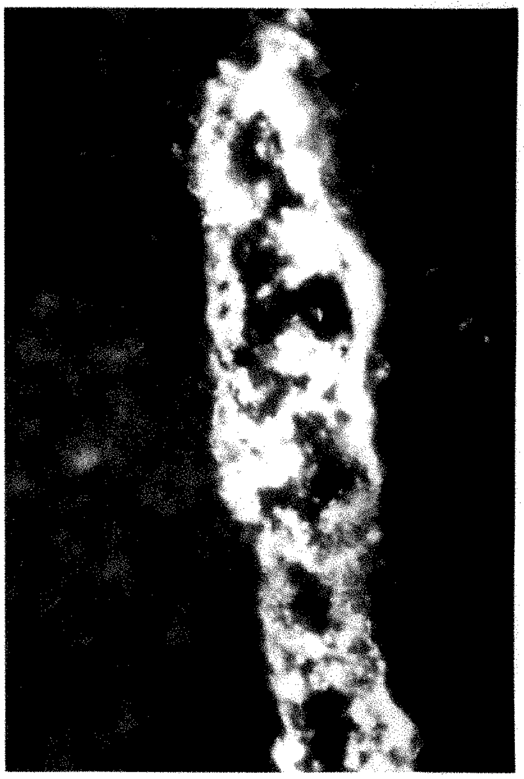

FIG. 7. Immune complex vasculitis. Fluorescent granules of IgM in a vessel wall. Immunofluorescent techniques are necessary to detect antigen, antibody and complement which cannot be seen in routine sections. × 400.

complexes are not inherently harmful, but by activating complement they attract polymorphonuclear cells and trigger the coagulation system.

Only certain sizes of complex localize in vessels. Those composed of more than two molecules of antigen and antibody are harmlessly degraded by macrophages in the liver and spleen (Haakenstadt and Mannik, 1974). Very small complexes are trapped in the capillaries of renal glomeruli, the lungs and the choroid plexus. It is the intermediate-sized deposits which localize in the walls of arteries, arterioles and venules. Other factors, such as increased arterial pressure and local vascular turbulence, have a bearing on where complexes lodge. Focal trauma, as in the vasculitic lesions in the buttocks in Henoch–Schönlein syndrome, and venous stasis are also important. Much of the current knowledge of immune complex vasculitis has been derived from experiments in which animals have been injected with antigen or antigen–antibody complexes (Cochrane and Koffler, 1973).

One of the major variables in the different clinical types of immune complex vasculitis is the size of the vessels affected (table VI). In many instances the antigenic component of the immune complex has not been identified. Furthermore, autoantibodies, which can play a pathological role in conditions such as systemic lupus erythematosus, are also found in other disorders in which they do not appear to form immune complexes.

There is another mechanism by which immune complexes can localize within vessel walls. If antigen is first deposited, circulating antibody may subsequently enter the vessel wall and fixation of complement may follow. This might well be the sequence of events in systemic lupus erythematosus.

In most immune complex disorders the pathological changes in the vessels are similar. A dense infiltrate of neutrophils or eosinophils is often present and is useful in distinguishing the lesions from those of malignant hypertension (fig. 8). Protein accumulates in the intima and media and both immunoglobulin and complement are usually detectable. The antigen, if known, should be demonstrable in the same position.

Complications of the vasculitis include thrombotic occlusion of arteries, arterioles and venules with resulting ischaemia or infarction. Multiple sites are usually involved at the same time and both skin and kidney are favoured targets. Inflammation and increased vascular permeability of capillaries causes petechial haemorrhages and haematuria (Henoch–Schönlein syndrome), whilst destruction of part of the wall of larger vessels leads to aneurysms (polyarteritis nodosa). Steroids have been the mainstay of treatment in most types of vasculitis. Recent evidence suggests that cyclophosphamide may be effective in severe polyarteritis nodosa (Fauci et al., 1979) and Wegeners granulomatosis (Reza et al., 1975).

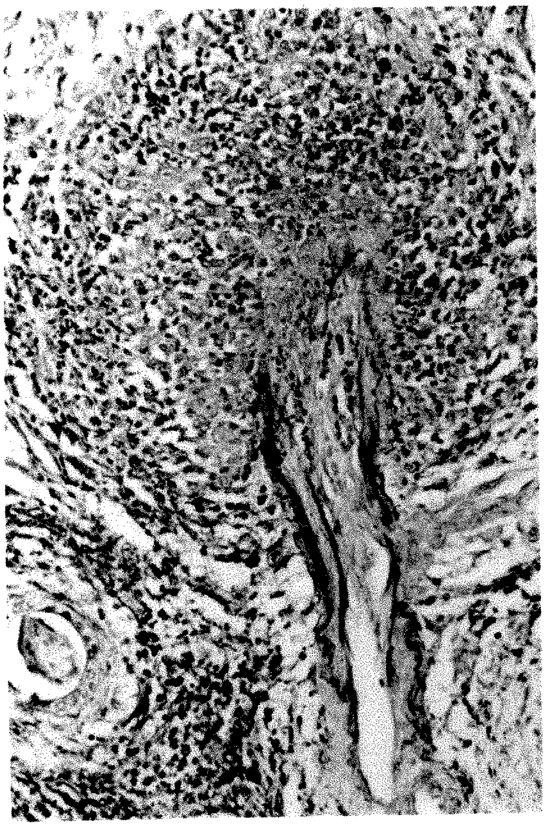

FIG. 8. Polyarteritis nodosa. This vessel was included in a liver biopsy of a 69-yr-old female. Marked polymorph, eosinophil and lymphocytic perivascular infiltration. The focal involvement of the vessel is characteristic. Reticulin. × 210.

VASCULAR DISEASES OF UNKNOWN AETIOLOGY

Cranial arteritis (temporal or giant cell arteritis)

Cranial arteritis was first recognized by Hutchinson, who in 1890 described an 80-year-old man who was prevented from wearing his hat by tender and inflamed temporal arteries. Although the arteries of the head and neck are most frequently involved, almost any part of the arterial

TABLE VI. *Features of immune complex vasculitis.* + = *sometimes affected;* + + = *often affected;* + + + = *invariably affected;* – = *not involved*

	Systemic lupus erythematosus	Rheumatoid vasculitis	Polyarteritis nodosa	Henoch–Schönlein Syndrome (anaphylactoid purpura)	Subacute infective endocarditis	Wegener's granulomatosis
Vessels						
Aorta	–	+	–	–	–	–
Muscular arteries	+	+	+ + +	+	+	+ to + +
Arterioles	+ +	+ + +	+	+	+	+ + +
Capillaries	+ + +	+ +	–	+ +	+ + +	+ + +
Venules	+	+	–	+ +	–	–
Composition of immune complexes						
Antibody	IgG, IgA and IgM	IgG, IgA and IgM	IgG, IgA and IgM	IgA, IgG and IgM	IgM, IgG	IgG, IgM
Antigen	DNA, RNA ? C-type virus	DNA in some cases	Hepatitis B in some cases	Not known	Many varieties of bacteria, fungi coxiella and chlamydia	Hepatitis B in some cases
Autoantibodies	Anti-DNA. Many others	Anti-DNA. Rheumatoid factor	No	No	No	No
Complement concns (C3 and C4)	Low in acute exacerbations	Low in acute exacerbations	Normal	Normal	Low	Normal
Circulating immune complexes	Yes	Yes	Yes	Yes	Yes	Not known

tree can be affected. Disease of the ophthalmic or posterior ciliary arteries can lead to blindness.

In florid clinical cases the superficial temporal artery is hard, tender and pulseless. Microscopically there is marked intimal thickening and a dense, sometimes granulomatous, chronic inflammatory and giant cell reaction. This is often centred in and around the elastic lamellae (fig. 9). It is conventional to confirm the clinical diagnosis by biopsy, but in our experience this is positive in less than 60% of apparently genuine cases which subsequently respond to steroid therapy (Allsop and Gallagher, 1981). Focal involvement of the superficial temporal artery by the disease is probably responsible for this high false negative rate. The aetiology of cranial arteritis is obscure.

Pulseless or Takayasu's disease is an exceedingly rare inflammatory disorder of the aorta and its major proximal branches. Most patients are young or middle aged females who present with ischaemic symptoms in the arms or head. Characteristically, there is a severe necrotizing arteritis. The histological similarity to giant cell arteritis, and to a lesser extent the vascular changes in the collagen disorders, raises doubt as to whether Takayasu's disease is a distinct pathological entity.

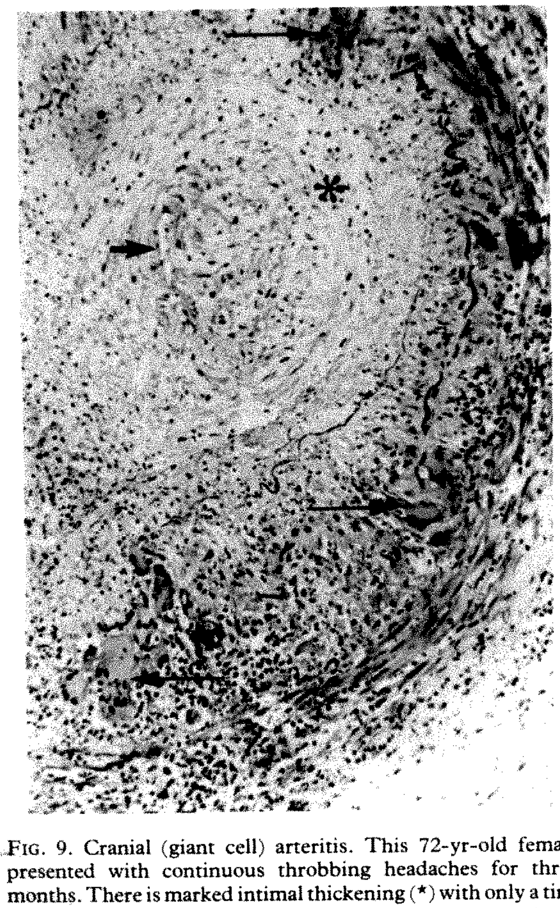

FIG. 9. Cranial (giant cell) arteritis. This 72-yr-old female presented with continuous throbbing headaches for three months. There is marked intimal thickening (*) with only a tiny residual lumen (short arrow). Giant cells (long arrows) are plentiful. Elastic–Van Gieson. × 200.

Scleroderma (systemic sclerosis)

The vascular changes of scleroderma are similar to those of benign or malignant hypertension, but only 20% of patients are hypertensive. Muscular arteries and arterioles are narrowed by newly formed layers of collagen and mucopolysaccharide. Protein deposits are frequently present, but are not invariable.

The cause of this curious disorder is unknown. Jayson (1977) has postulated an abnormality of collagen synthesis. Although circulating autoantibodies to RNA and DNA are present in most patients there is no evidence that immune complexes are deposited.

Buerger's disease (thrombangitis obliterans)

This rare disease is more strongly associated with smoking than any other vascular disorder. Most patients are young males; Jews are affected twice as commonly as non-Jews. The clinical picture is often distinctive. Peripheral gangrene develops in the fingers and toes, but the changes are progressive and serial amputations are often required.

The pathological alterations are less specific, particularly in patients older than 45–50 years. Small arteries are primarily involved and show marked intimal fibrosis and thrombus formation. In the cases we have seen the media was relatively normal and the necrosis so characteristic of atherosclerosis was absent. Apart from the striking association with heavy smoking, little is known of the aetiology of Buerger's disease.

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CLINICAL MANIFESTATIONS OF VASCULAR DISEASE

BRIAN KIRBY

Most middle-aged people in Western society harbour atherosclerosis somewhere in their body, but few of them are aware of it until, either insidiously or abruptly, it reduces the blood supply to an important organ to less than that necessary for its function. If atherosclerosis was a disease confined solely to older patients in their waning years, the immense research endeavour devoted to it would be questionable, but this is not the case. Even making allowances for fashions in diagnosis, the condition has become commoner during the past 50 years, so that today it is the largest single health problem afflicting developed nations. Inevitably, anaesthetists will encounter patients with atherosclerosis in the course of their daily practice, quite apart from those undergoing vascular surgery. Almost every organ in the body can become involved by interference with its blood supply. Fortunately one site tends to predominate in any individual patient. Three sites are of outstanding importance, namely the heart, the cerebral circulation, and the aorta and peripheral vessels. Why atherosclerosis should have a predilection for certain sites is a question as intriguing for the clinician as for the experimental pathologist. The patchy nature of atherosclerosis is of practical importance as it allows restoration of blood supply to an organ by by-passing a narrowed arterial segment, something which would be impossible if arterial calibre was uniformly narrowed throughout the whole of its length. However, finding atherosclerosis at one site should alert the clinician to the likelihood of its presence elsewhere. It is no service to the patient to treat the ravages of the disease in one organ and fail to try to halt its inexorable progress elsewhere in the body.

RISK FACTORS IN ATHEROSCLEROSIS

Unlike many other diseases no single cause has yet been found for atherosclerosis. Largely as a result of pioneering efforts involving those living in the small town of Framingham in the United States, a number of features associated with the disease have been discerned (Kannel, McGee and Gordon, 1976). Less extensive, but equally contributory studies elsewhere have confirmed the association between atherosclerosis and a number of what are termed "risk factors". These "risk factors" are not the *cause* in the same sense in which the pneumococcus *causes* pneumonia, but the association is so strong that removing risk factors appears to reduce the chance of developing atherosclerosis. There is early, but nonetheless, significant evidence of a decreasing mortality from atherosclerosis in the United States, where considerable public attention has been paid to dealing with these risk factors. In general no harm is likely to arise by recommending appropriate measures in asymptomatic subjects (primary prevention) and to those with clinically apparent disease (secondary prevention). We do not know if eliminating these risk factors will eradicate atherosclerosis entirely. It is probable there are as yet undiscovered aspects to the disease and attention to risk factors deals predominantly with a "high risk" group; nonetheless primate experiments and serial observations in man suggest regression of atherosclerosis following some of these measures (Malinow, 1980). The most important risk factors are:

Smoking
Arterial pressure
Diet
Lipid metabolism
Physical activity
Obesity

These risk factors, common to all patients with atherosclerosis, warrant appropriate advice.

The risk from *cigarette smoking* is proportional to the daily consumption. Exactly how cigarette smoking increases the risk of developing atherosclerosis is unknown. The increased risk in non-smokers exposed to a smoke-filled environment suggests something in the smoke rather than an association between personality, smoking and atherosclerosis as has been suggested. Carbon

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monoxide or one of the many chemical constituents of smoke are the most likely culprits. Communities consuming a *diet* rich in animal or saturated fat tend to have a higher cholesterol intake and a significantly higher mortality from atherosclerosis. Confusion has arisen because an individual within the community may have a level of cholesterol conventionally regarded as within the "normal range", yet such a subject may have a higher risk when compared with somebody in another community which has a lower overall risk. There are, of course, other subjects with abnormally increased cholesterol as a result of abnormal lipid metabolism (see below). Combining the knowledge about cholesterol values in communities and individuals with the finding of rich deposits of cholesterol in atherosclerotic plaques led to the "lipid hypothesis". It proved relatively simple to demonstrate in man and other animals a relationship between increased cholesterol concentrations and atherosclerosis, but much more difficult to prove the hypothesis by demonstrating a reduction in morbidity and mortality by reducing cholesterol. Persuading patients to alter their diet for several years proved difficult, therefore there has been considerable interest in the support for the hypothesis derived from a study of the lipid lowering drug, clofibrate. Approximately 17 500 men participated in a double-blind controlled trial for 5–8 yr. Unfortunately, the evidence for a reduction of atherosclerosis was marred by an increase in bowel cancer and biliary disease (Report from the Committee of Principal Investigators, 1978). Whether this was specifically caused by the drug clofibrate or whether dietary modification would have a similar effect is debateable (Kirby, 1979). Currently there is considerable and, at times, vitriolic debate about national recommendations to reduce saturated fat intake (mainly dairy produce in Britain), but the consensus of national committees supports the idea of recommending dietary modification. In the United Kingdom the dissenting view has been cogently argued by McMichael (1979).

Lipid concentrations in the blood are determined by the amount of fat absorbed from the gut and by endogenous synthesis of lipids in the liver. Lipid metabolism entails transport of relatively insoluble cholesterol and triglycerides by the blood. These lipids are transported as complex molecules called lipoproteins which consist of a protein (apoprotein) and variable amounts of cholesterol and triglyceride. The different lipoproteins which are formed along the metabolic pathway can be identified by chemical analysis, by measuring their density, or by their mobility on electrophoresis. This diversity of measurement techniques has caused confusion in nomenclature. A number of patterns have been discerned and form the basis of the Fredrickson–W.H.O. classification. This classification will some day be supplanted as it classes together genetically determined disorders of lipid metabolism with acquired disorders. However, for the moment it forms a useful basis in clinical practice for giving practical dietary or pharmacological advice to the individual patient (Fredrickson, Goldstein and Brown, 1978). There are no clinical features, apart from the rare appearance of xanthomata to alert the clinician to the presence of a lipid disorder. A patient with atherosclerotic disease needs to have the fasting blood lipid concentrations measured. The discovery that increased concentrations of high density lipoprotein (HDL) seems to confer protection from atherosclerotic disease (Miller and Miller, 1975) could revolutionize this field either if drugs are found to stimulate HDL formation or if synthetic HDL is manufactured, but first much more information about HDL is needed. For example women on oestrogens (for example contraceptive pill) have increased HDL concentrations yet, paradoxically, they have an increased morbidity from atherosclerotic disease (Gordon et al., 1977).

Life assurance companies have long appreciated the ominous risk to life posed by *high arterial pressure*. Accelerated atherosclerosis contributes to this mortality, although other aspects such as cerebral haemorrhage are of equal importance. There is no sharp cut-off point below which the risk is zero; with each increment in pressure, even within the commonly accepted normal range, the risk increases (Kirby, 1980).

Few jobs nowadays entail vigorous *physical activity* and few people continue regular exercise after leaving school. Comparing a group of sedentary workers who exercise vigorously (that is feeling breathless and sweating—submaximal exercise) in their leisure time with others who do not do so, the risk of developing coronary disease is lower (Morris et al., 1980). Stimulation of HDL by exercise seems to confer the protection (Wood and Haskell, 1979). Whether the present craze for jogging, much of which is relatively mild exercise, will reduce the frequency of coronary disease is unknown. Apart from potential protection from atherosclerosis, exercise has other physical and psychological benefits.

Obesity is common in adults and children in our affluent society. Apart from its association with diet, lipid metabolism, high arterial pressure and exercise, it seems to be a risk factor in its own right.

Correction of these risk factors is unlikely to be deleterious even in the asymptomatic individual, and many, for example high arterial pressure, warrant treatment in their own right.

ANGINA

Angina is often described by patients as a tight or pressure feeling deep within the chest radiating to the lower jaw and to the inner border of the left arm precipitated by effort and subsiding promptly on resting. The character of the pain and its relationship to activity are the two most important features when it comes to sorting out the atypical cases. The wide variety of precipitating factors is best understood in terms of cardiac physiology. Although the myocardium can temporarily survive fluctuating concentrations of metabolic substrate, it does not have the same margin of adaptability to oxygen lack as skeletal muscle. Normally, myocardial blood supply increases to keep pace with myocardial oxygen consumption. Limitation of coronary blood flow by atherosclerosis means that anything increasing myocardial oxygen consumption is likely precipitate angina. Heart rate and arterial pressure are the two major determinants of myocardial oxygen consumption. Thus anything increasing either of them tends to precipitate angina. Obvious examples are dynamic exercise and anxiety, but less obvious are the physiological response to cold or the response to static (isometric) exercise. Mild handgrip, say 30% of maximum (equivalent to holding 10 pounds in weight), increases heart rate and arterial pressure in all subjects; the greater the effort, the greater the response. Most of us use similar activity many times a day and its role in angina is often forgotten. Generally, once the stimulus is removed angina subsides rapidly and it rarely lasts longer than 15 min. Anxiety set off by an attack of exercise-induced angina can perpetuate it.

The diagnosis can be established in some patients with a clear history, by finding minor abnormalities indicative of myocardial ischaemia on the resting electrocardiogram, but more often an electrocardiogram recorded during exercise showing 2 mm of ST segment depression is needed to establish the diagnosis. Artificially increasing heart rate by pacing is an alternative less frequently used now that direct visualization of the coronary vessels is more widely available. Assessment of the equivocal case is much easier with coronary arteriography and radioisotope visual imaging. One result of the wider use of these techniques has been the discovery of coronary spasm (Hillis and Braunwald, 1978). Prinzmetal hinted at this possibility many years ago when he described atypical angina mainly occurring at rest in women less than 50 years of age (Prinzmetal's variant angina). Current studies suggest this is commoner than hitherto anticipated. An individual with coronary spasm may respond best to a calcium antagonist drug such as nifedipine. To the epidemiologist this discovery is of immense importance when it comes to following the natural history of the disease as there is no clinical way to differentiate coronary spasm from coronary atherosclerosis.

MYOCARDIAL INFARCTION

Pain of a character similar to angina, but more severe and persisting for more than 30 min at rest should alert the clinician to the possibility of myocardial infarction. Sometimes the diagnosis of myocardial infarction is made retrospectively in a patient who gives no history of chest pain. This is uncommon. The diagnosis can be unequivocally established by the electrocardiogram. Often the earliest electrocardiogram does not show all the features of myocardial infarction although, within 72 h most that are going to show abnormalities do so. Ancillary confirmatory evidence of myocardial infarction can be derived from the serum enzymes. Creatine phosphokinase (CPK) is usually increased within 4–6 h of the onset. Serum glutamic oxaloacetic transaminase (s.g.o.t.) increases later at around 24 h, but subsides rapidly. Unless there are urgent reasons for establishing the diagnosis, neither of these tests are used routinely as they are expensive in terms of laboratory technician time. The lactic dehydrogenase concentration increases slowly after myocardial infarction, reaches a peak at about 48 h and subsides equally slowly. Its peak activity corresponds to the point where equivocal serial electrocardiograms may leave the clinician with some doubt—hence its popularity as a final arbiter for the presence of myocardial infarction. Roughly one-third of those with proven myocardial infarction have no clinical signs whatsoever, but the remaining two-thirds develop one or more complications: disturbed cardiac rhythm, cardiac failure and cardiogenic shock. Following the introduction of electrocardiographic monitoring it became apparent that the majority of patients had ectopic beats; however, subsequent experience of monitoring normal subjects indicates they too have a surprisingly large number of ectopic beats. Clearly some ectopic beats are more benign than others. The early hope of reducing mortality by coronary care units established for electrocardiographic monitoring has failed to materialize (Hill, Hampton and Mitchell, 1978). Whilst it is true that an ectopic beat coming early after the preceding beat ("R-on-T ectopic") or runs of ventricular ectopic beats may precede the development of ventricular tachycardia or ventricular fibrillation, these may start without any warning whatsoever. Community-based studies show that 50% of patients with myocardial infarction die within the first hour of the onset of symptoms. Because of delays in seeking advice or arranging admission, several hours often elapse before admission to a coronary care unit (Armstrong et al., 1972); this means that the period of highest risk has passed before admission. Enthusiasts have explored the possibility of earlier care using specially equipped ambulances or advocated the immediate administration of anti-arrhythmic drugs. Neither approach has proved to be fully satisfactory. Roughly half the patients admitted in the conventional manner turn out to have myocardial infarction, the remainder have a variety of other conditions causing chest pain. Unnecessary admission, with the anxiety it induces and the use of potent drugs, is harmful and the cost is considerable. Coronary care units have a definite part to play in coping with the complicated case, especially those needing cardiac pacing until the return of normal atrioventricular conduction. The valuable stimulus of coronary care units to research should not be ignored.

Minor degrees of left ventricular failure can be detected by hearing crepitations at the lung bases or by detecting a third or fourth heart sound. A chest x-ray showing distension of upper lobe vessels, indicating reversal of the normal pattern of pulmonary perfusion, is a sensitive indicator of left ventricular failure (Tattersfield et al., 1969). Frank pulmonary oedema is less common, tending to occur in those with pre-existing myocardial damage. It is especially ominous when associated with hypotension. Cardiogenic shock still has a high mortality of 85% no matter what treatment is used. Malfunction of the myocardium interfering with the heart's pumping ability is the primary disorder, but animal experiments and observations in man have revived the suggestion of a contribution from disordered autonomic nervous function (Kirby, 1977).

STROKE

Because of the difficulty in differentiating cerebral thrombosis from haemorrhage or embolus on clinical grounds alone, the term "stroke" is now widely used. Robson (1980) has discussed the problems this poses for the epidemiology of cerebrovascular disease. Wider experience of non-invasive techniques such as computerized axial tomography may resolve these problems. Doubt continues to cloud the precise aetiology of cerebral haemorrhage, but it is generally agreed to be a result of rupture of small aneurysms (Charcot–Bouchard aneurysms) by high arterial pressure. Without denying the part atherosclerosis could play in weakening cerebral vessels in hypertensive patients, it is more clearly and directly related to cerebral haemorrhage. In view of current hopes for stroke prevention there is great interest in cerebral thrombosis.

Like that to other organs, cerebral blood supply may be either diminished or absent, but unlike other organs the brain has no margin of reserve. The brain is highly dependent on an uninterrupted supply of oxygen and glucose, in contrast to the lower limb, for example. Exercising skeletal muscle can continue functioning anaerobically and has stocks of metabolic substrate on which it can call when blood supply fails to keep pace with metabolic demand. This happens during vigorous exercise, but the anaerobic debt is repaid at the end of exercise with no damage to the muscle. This is not the case with the brain as there are no mechanisms for anaerobic metabolism and the metabolic reserves of the brain are paltry. Even temporary reduction in blood supply to the brain produces symptoms and signs and failure to restore blood supply results in permanent damage. With an organ fulfilling functions as diverse as the integration of autonomic nervous function in the brainstem to the higher intellectual functions of the cortex, it comes as no surprise to find a bewildering diversity of clinical features. One advantage of this variety of clinical findings is the precision with which a lesion can be localized by anyone with a knowledge of neuroanatomy. Fortunately for the non-specialist, most patients have a lesion in one of a small number of common sites producing either a transient ischaemic attack (TIA) or a fully developed stroke.

Transient ischaemic attack

Definition of a transient ischaemic attack differs from one author to another, but in general it denotes the rapid onset of neurological symptoms over minutes and their persistence for up to 3 h (some say up to 24 h.) Complete recovery is usual. By the very nature of the episode the disordered physiology is speculative. Either thrombosis rapidly followed by lysis or temporary platelet aggregation underly an episode. Normally, collateral circulation through the circle of Willis should be able to maintain blood supply when a major vessel is occluded, but these patients often have widespread atherosclerosis demonstrable on cerebral arteriography (Ueda, Toole and McHenry, 1979). Hence any occlusion of a major vessel results in cerebral ischaemia. Any cerebral vessel may be involved, but two territories are predominantly concerned: the carotid and vertebro–basilar territories.

Involvement of the carotid territory produces weakness of the arm and leg on the opposite side and often numbness as well. If the dominant hemisphere (left hemisphere in right handed subjects) is involved, dysphasia is common. If the patient is examined during an attack the physical signs would be those of a hemiplegia, but most clinicians working in a hospital are unlikely to encounter a patient until the signs have passed off. When the vertebro–basilar territory is involved the symptomatology is different. Weakness may involve anything from one to four limbs. Homonymous hemianopia is common, as is nystagmus. Dysarthria, vertigo, ataxia of gait or limbs are common. Dizziness or vertigo are common complaints in these patients although a patient presenting with this complaint alone, and no other neurological symptoms or signs, is more likely to have one of the many other causes of vertigo. Drop attacks, or sudden falls with loss of muscle tone, but without loss of consciousness are virtually pathognomonic. The diversity of symptoms, some of which sound bizarre, coupled with the absence of objective signs when the patient visits a doctor can trap the unwary clinician into dismissing them. Greater awareness by the profession and wider public education are needed if stroke prevention is to prove practicable.

Roughly half those with transient ischaemic attacks have a bruit. When present it is a valuable confirmatory sign of cerbrovascular disease, but it is a poor localizing sign of the site of major obstruction (Ueda, Toole and McHenry, 1979). Sometimes evidence of extracranial carotid obstruction can be derived from comparison of the intraocular pressure on one side with the other. The non-invasive technique of ophthalmodynamometry is valuable in assessing patients as cerebral arteriography has small but definite hazards and the number of patients involved is large.

Much of the emphasis on this subject would be misplaced but for the current interest in preventing strokes. Half of those sustaining a fully developed stroke give a history of premonitory transient ischaemic attacks. Using currently available methods roughly half of these strokes could be prevented (that is, one quarter of the original group). In any trial where there is no definite end-point such as death, or full recovery, evidence for the efficacy of any treatment is difficult to obtain; when the criteria for admission to the study are also controversial it is not in the least surprising to find therapeutic controversy. In spite of this, measures to prevent platelet aggregation appear to be a valuable new therapeutic tool (McDowell, Millikan and Goldstein, 1980).

Fully developed stroke (cerebral thrombosis or infarction)

When the symptoms and signs referred to already become permanent this is regarded as a fully developed stroke. The patient may lose consciousness, but more often with cerebral thrombosis becomes drowsy or confused. The physical signs of a hemiplegia are common and well known but brainstem infarction is often less well understood. Central nystagmus, hyper-reflexia, internuclear ophthalmoplegia, homonymous visual defects, dysarthria, disorders of co-ordination or cerebellar function are commonly found. The importance of bruits has been alluded to already; their absence does not rule out cerebrovascular disease, but their presence is valuable confirmatory evidence. It is often impossible to carry out a complete examination of the nervous

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system in the early stages as many aspects of the examination require full co-operation from the patient. Re-examination is valuable in confirming equivocal signs and in making an early assessment of the chances of recovery. With a hemiplegia recovery starts first in the proximal muscles of the lower limb and later with the more distal muscles. The arm recovers later and less fully. Evidence of recovery within the first few days indicates a likelihood of eventual recovery of much function. Recovery depends on the hemisphere involved; loss of function in the non-dominant hemisphere can be especially problematical because it produces less obvious cortical signs, yet the loss of body image (apraxia) is as difficult to overcome as is limb weakness.

Not all cerebral thromboses are catastrophic. Sometimes the lesion is localized to the cortex, producing dysphasia. Increasingly it is appreciated that infarction deep within the brain substance may produce lacunes, but little by way of clinical signs (Hachinski et al., 1975). Intellectual deterioration (dementia) may be the only manifestation of cortical involvement and in its earliest stages it may be so subtle as to escape detection.

PERIPHERAL ARTERIAL DISEASE

Whilst any vessel in the body may be affected by atherosclerosis, the aorta and lower limb vessels are involved more often than elsewhere.

Aorta

Aneurysmal dilatation and rupture are the commonest problems. Three-quarters of aortic aneurysms are confined to the abdomen. Most of these are asymptomatic, being found on routine examination or radiology. Symptoms, when they arise, are often ill-defined and confused with other causes of back or abdominal pain. Back pain can be differentiated from musculo–skeletal causes by the lack of aggravation produced by movement. When symptoms are present surgical relief is often needed, but more problematical are asymptomatic cases. Dissection or rupture are likely within 1 year of diagnosis in half those patients with an aneurysm greater than 6 cm in diameter compared with only 15% with a smaller aneurysm (Szilagyi et al., 1966). Thus a rational decision about surgery can be made in the asymptomatic individual. Aneurysmal size can sometimes be assessed clinically or from a lateral x-ray of the abdomen, where calcification within the aortic wall enables measurements. Ultrasound in the B-scan mode is more accurate and increasingly used; it can also be used for thoracic aneurysms. Whole body computerized axial tomography is not yet widely available, but may prove an even more valuable non-invasive method for assessing aortic diameter at any point along its length (Fulton et al., 1980).

Lower limb vessels

Intermittent claudication, a dull, constricting pain experienced in the exercising muscle group distal to the site of arterial obstruction, is the commonest symptom. Characteristically, this is felt in the calf muscles after walking 200–300 yards and it passes off with rest. Similar pain can be experienced in other muscle groups, for example in the buttock with iliac artery obstruction. The metabolic reserve of exercising skeletal muscle has been referred to already. Because of its carbohydrate reserve and ability to continue working anaerobically, severe narrowing may be present before symptoms warrant medical advice. Pain may also arise at rest when obstruction is severe. The pain is obdurate and often interferes with sleep. Ischaemia of peripheral nerves (ischaemic neuropathy) is another cause of a constant or paroxysmal pain in peripheral vascular disease.

Diminution or absence of the peripheral pulses above the level of the pain is the most important physical finding. Confidence in diagnosing *absence* of a pulse can only be achieved by taking every opportunity to seek the *presence* of pulses in unaffected subjects. Even then trained observers may disagree about the physical signs. Colour and temperature changes may be helpful in the resting limb, but pallor on elevation made worse by exercise of the limb raised above heart level and delayed venous filling on lowering the limb are useful additional guides to the presence of peripheral vascular disease. Marked reactive hyperaemia on lowering a limb with impaired blood supply occurs because of accumulation of vasodilator metabolites. Severe impairment of blood flow can cause trophic changes, especially in the toes.

Using a Doppler flow meter at the ankle as a sensitive stethoscope it is possible to use a thigh pressure cuff to compare arterial pressure in the leg with arm arterial pressure; normally the ratio of pressure at the ankle to that in the arm is equal to, or greater than, 1.0. In symptomatic peripheral vascular disease it is about 0.5 and in severe cases less than 0.5. Most patients need no more than clinical and non-invasive investigations, but when surgery is contemplated more accurate information about the site and extent of the block is necessary. Arteriography carries a risk, but a justifiable one, for such patients as non-invasive techniques are ineffective at most sites in the lower limb.

Complete arterial occlusion is an emergency. If carried out soon enough, endarterectomy may restore the circulation, but this is not always possible because of the time elapsed or the site of occlusion. Pain is variable, but the limb below the site of occlusion is cold, pulseless and pale with dusky cyanosis. Sometimes the limb remains viable as a result of rapid dissolution of the thrombus or because of an adequate collateral circulation. When part of the limb is no longer viable and amputation becomes necessary it should be carried out at a level where healing is likely to be good. Nothing is more soul-destroying for a patient than losing a limb piecemeal for failure to amputate the limb through viable tissue. In the case of the lower limb above-knee or through-knee amputation often gives the best chance of early healing and rapid rehabilitation.

CONCLUSION

Atherosclerosis has been likened to an epidemic affecting Western society. Now that there are signs of it abating in North America the metaphor is even more apt. We resemble the physicians of the 19th century facing epidemic diseases unaware of their bacterial nature, but knowing the efficacy of good sanitation without knowing the reasons why. If these early trends prove correct, perhaps by the next century an issue devoted to vascular disease will be as irrelevant as issues devoted to smallpox and cholera are today.

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DRUG THERAPY OF HYPERTENSION AND ISCHAEMIC HEART DISEASE

A. J. MARSHALL

HYPERTENSION

Uncomplicated hypertension is a symptomless condition. It is often discovered at a routine examination and is not infrequently found during assessment before operation. The patient who has untreated severe hypertension is at greater risk during anaesthesia and surgery than the patient with normal arterial pressure. It is ideal for the hypertensive patient to be taking effective and stable drug therapy (Prys-Roberts, 1980).

Who to treat

Everyone agrees that it is correct to treat those patients who present with the accelerated phase of hypertension (Grade III or IV retinopathy) or with evidence of important hypertensive complications. The clear benefits of treating severe hypertension are a reduced frequency of hypertensive cardiac failure, prevention of the advent of the malignant phase or reversal of the manifestations of established malignant hypertension and a reduction in the frequency of strokes.

Does the benefit extend to slightly increased arterial pressure? Insurance statistics show that mortality and morbidity increase progressively with increasing values of arterial pressure. The increased risks start with even modest increase of pressure and to live longest, the lower the arterial pressure the better. However, whether treatment influences the outcome of such patients is still not clearly proven. In Britain the Medical Research Council has organized a randomized controlled trial of treatment of mild hypertension. Adults with diastolic values between 90 and 109 mm Hg (Korotkoff 5th phase) are being followed for 5 years to determine the effect of treatment. The results are awaited. Two other trials have been reported recently and do suggest that treatment is worthwhile. The Australian Therapeutic Trial in Mild Hypertension (Report of the Management Committee, 1980) is a study of 3427 men and women with a diastolic pressure between 95 and 109 mm Hg. They were given either active or placebo treatment and followed for 4 years. There were four cardiovascular deaths and 82 non-fatal end-points in the actively treated group compared with 13 deaths and 108 non-fatal end-points in those who received placebo. The Hypertension Detection and Follow-up Program Cooperative Group (1979) studied 10940 patients, of whom 71% had a diastolic pressure of 90–104 mm Hg. They found a 17% reduction in mortality in those treated, presumably very effectively, in special blood pressure clinics.

At present I think no absolute advice can be given and the decision whether or not to treat mild hypertension remains one to be made after assessment of each individual patient. It will be based on the arterial pressure, but is influenced by the patient's age, a family history of hypertensive disease and early death, and the weighting of side-effects of currently available drugs against possible benefits of therapy.

Lability of arterial pressure

In these considerations it should be remembered that there are marked physiological variations in both systolic and diastolic pressures of normal people during the course of any day. Continuous intra-arterial recording shows that the ranges of these may be 100 mm Hg systolic pressure and 40 mm Hg diastolic pressure. The average diurnal variation is 33 mm Hg systolic and 10 mm Hg diastolic pressure. Acute stress and fear are two potent stimuli which will cause an increase in pressure. Thus, the house surgeon may find that a patient's pressure is high when he admits him to hospital, but should not immediately deduce that this necessitates hypotensive treatment. When the patient is calmer the arterial pressure may decrease to normal. If possible repeat measurements are called for to establish a true baseline. Treatment, once started, is often life-long.

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Investigation

The retinae should be examined, an electrocardiogram recorded and plasma urea measured in all patients to establish the extent of hypertensive damage. Further detailed investigation is not usually rewarding. However, some simple things can be done to help exclude a detectable underlying cause.

Enquiry about drugs

There is an increased frequency of hypertension in women who are taking the oral contraceptive pill (Oral Contraceptive Study of the Royal College of General Practitioners, 1977). Hypertension is usually reversible if the pill is stopped. Carbenoxalone sodium and liquorice may increase pressure because of mineralocorticoid activity, and analgesics, if taken in large quantities over a prolonged period, can cause renal papillary necrosis and secondary hypertension.

Plasma electrolytes

The clue to primary aldosteronism (Conn's tumour) is the combination of a high sodium concentration (>140 mmol litre^{-1}), a low potassium concentration (<3.2 mmol litre^{-1}), and a high bicarbonate concentration (>30 mmol litre^{-1}) in plasma. The clinician will have to decide whether to proceed with further investigation of the renin–aldosterone system in the hope of finding a discreet adrenal adenoma which can be removed surgically.

Urinary catecholamine estimation

If possible, I recommend that all hypertensive patients collect a 24-h urine specimen for catecholamine estimation so that a phaeochromocytoma can be excluded. The diagnosis is not always obvious from the history. It is important because, if missed, conventional hypotensive therapy can precipitate an acute pressor crisis. Beta-adrenoceptor blockade should not be given to a patient with a phaeochromocytoma because this results in unopposed alpha activity causing vasoconstriction and an alarming pressure increase. Anaesthesia and surgery are hazardous in patients with phaeochromocytoma and may prove fatal if the diagnosis is unsuspected.

I.v. pyelography

This is not an essential routine investigation because it seldom alters management, is expensive and occasionally unpleasant for the patient. Full renal investigation, including arteriography, should be reserved for those patients in whom there is a strong suspicion of the "curable" renal cause of hypertension—renal artery stenosis. This particularly means young hypertensive women who may have fibromuscular hyperplasia of the renal artery. Renal investigation is also warranted in patients who fail to respond to conventional medical treatment (if, of course, the patient is actually taking the prescribed drugs!).

Principles of medical treatment

(1) Confirm sustained hypertension.
(2) Document existing hypertensive complications.
(3) Consider the possibility of a potentially curable underlying cause.

(4) *General measures*

Patients should stop smoking and, if necessary, lose weight. Otherwise they should be encouraged to live normally. Salt restriction is much debated. A marked reduction in dietary salt intake will decrease arterial pressure but is intolerable and not a practical possibility. It is not established that more modest reductions in intake will have a useful effect (Swales, 1980). Salt restriction should not be pressed on patients.

(5) *Long term drug therapy*

(a) There is no way of predicting the response of a particular patient to any one type of treatment. For instance, we found that the decrease in mean arterial pressure of 40 patients treated with oxprenolol was from 0 to 40 mm Hg. There was no separation into response groups (Barritt and Marshall, 1977). Early evidence which suggested that plasma renin activity might predict response to either beta-adrenoceptor blockade or diuretic therapy has since been shown to be incorrect. Treatment remains a matter of trial and assessment.

(b) Drugs should be given one at a time so that the effect of each can be assessed. A treatment which appears to have little or no effect should be withdrawn. If it produces some, but inadequate, pressure decrease then others should be added. Care should be taken with the dose response of each agent. It is often more sensible to add a second agent than to go on increasing the dose of the first (for example, the dose–response curve for bendrofluazide is flat above 5 mg daily. Doubling the dose above this will have no additional effect).

(c) All arterial pressure measurements should be made in a controlled manner so that the decisions outlined can be made sensibly.

(d) Treatment should be tailored to suit the patient and to keep side-effects to a minimum. Table I shows the ranking order of drugs that I favour.

TABLE I. *Drugs for treatment of hypertension—a ranking order*

Step 1	Beta-blocker OR Thiazide diuretic
Step 2	Combine beta-blocker and diuretic
Step 3	Add third agent: Centrally acting OR vasodilator e.g. methyldopa e.g.hydrallazine, prazosin
Step 4	Give these four treatments together
Step 5	Resistant hypertension Consider: (a) Adrenergic neurone inhibiting drug (b) Minoxidil (c) Captopril (Remember failure may be because the patient is not taking treatment)

(e) Treatment will only be effective if the drugs are taken. Asymptomatic patients find good drug compliance difficult over a prolonged period. Success comes with simple treatment regimes (particularly avoiding midday medication), health education and freedom from drug-induced side-effects.

(6) *Monitoring*

The effects of therapy should be monitored. The electrocardiographic signs of left ventricular hypertrophy will regress (fig. 1) and retinal haemorrhages and exudates disappear if the arterial pressure is decreased adequately.

Hypertensive emergencies

The reduction of increased arterial pressure within a few minutes is rarely indicated, undertaken too often, and may be dangerous.

In man, the cerebral circulation is autoregulated. In normotensive individuals cerebral blood flow remains constant despite the major variations in arterial pressure which occur during every day. However, in patients with long-standing severe hypertension this autoregulation pressure range is reset to a higher level, and cerebral perfusion may decrease if the arterial pressure is reduced immediately into the normal range. Symptoms of cerebral hypoperfusion can occur when the mean arterial pressure is reduced by about 50%—a severely hypertensive individual with a pressure of 220/140 mm Hg can be affected if the pressure is rapidly reduced to 110/70 mm Hg. With a slower reduction of pressure the lower setting for cerebral autoregulation readjusts back to normal so that the risk of hypoperfusion of the brain is much less.

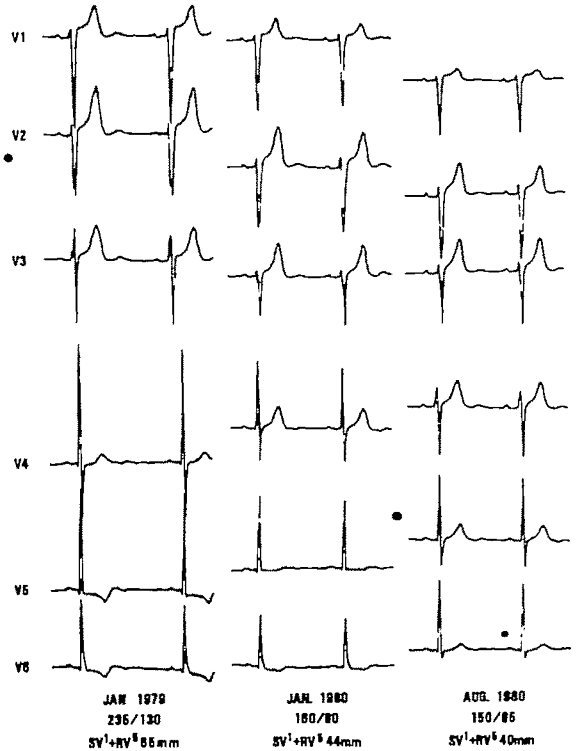

FIG. 1. The electrocardiograms of a 52-yr-old man with severe hypertension. The expected resolution of the changes of left ventricular hypertrophy as a result of hypertension is shown.

The clinical consequences of sudden reduction of arterial pressure have been described by Ledingham and Rajagopalan (1979). Ten patients with accelerated hypertension were treated with i.v. diazoxide to reduce pressure rapidly. All developed neurological damage and three died. Ischaemic damage was found in their brains. Hulse, Taylor and Dillon (1979) have reported three children who developed major permanent neurological deficits and Cove and others (1979) described two young women who became blind with rapid reduction of increased arterial pressure to normal values.

Malignant hypertension should be treated promptly and effectively, but I recommend that this is usually best achieved with a combination of oral hypotensive therapy and bed rest. Beta-receptor antagonists, thiazide diuretics, vasodilators and methyldopa have a full effect in 24 h and the desired pressure decrease can be expected to result gradually in this time. Hypertensive encephalopathy is a rare condition but, again, I would reduce pressure over hours rather than minutes and control the fits with i.v. diazepam.

Indications for immediate reduction of pressure are the acute hypertensive crises seen with the following:

Phaeochromocytoma. Arterial pressure is usually controlled with an i.v. injection of phentolamine 5 mg and thereafter by a combination of alpha- and beta-adrenoceptor blocking agents given orally. I.v. labetalol has been used successfully.

Clonidine-withdrawal rebound hypertension. The rebound syndrome resembles a phaeochromocytoma crisis with outpouring of catecholamines. It can be managed with either i.v. injection of clonidine or by alpha- and beta-adrenoceptor blockade.

Interaction of *mono-amine oxidase* inhibitors and foods containing tyramine.

Eclampsia of pregnancy.

Dissection of the aorta.

Intravenous hypotensive agents which may be used are diazoxide, sodium nitroprusside, hydrallazine and labetalol.

Specific drugs

Beta-adrenoceptor blocking agents

The first choice agent for treatment of hypertension is usually either a beta-adrenoceptor blocker or a diuretic. Both have specific side-effects and each may therefore be contraindicated in some patients (table II). Some clinicians prefer a beta-receptor antagonist because of the possibility, as yet unproven, that they may confer some protection against myocardial ischaemia. Certainly they have an anti-arrhythmic activity which can be an advantage in the hypertensive patient facing anaesthesia. Beta-receptor blockade is of course particularly suitable for a patient with increased arterial pressure and angina pectoris.

The decrease in arterial pressure produced by these agents is a part of the competitive blockade of beta-adrenoceptors and is unrelated to the ancillary pharmacological properties. These are: cardioselectivity (their relative capacity to block effects on cardiac ($beta_1$) receptors or $beta_2$ (lung and blood vessel) receptors, partial agonist activity (intrinsic sympathomimetic activity) and membrane-stabilizing or local anaesthetic activity.

TABLE II. *Side-effects of beta-receptor antagonists*

Side-effect	Contraindicated in these patients
Bradycardia (usually does not worry the patient)	1. Sino-atrial disease 2. Reduced atrio-ventricular conduction
Reduced cardiac output	1. Left ventricular failure 2. Peripheral vascular disease, intermittent claudication
Raynaud's phenomenon (common side-effect)	1. Avoid if Raynaud's is severe or peripheral gangrene
Bronchial constriction	1. Asthma 2. Chronic airways disease
Interference with recovery mechanisms from hypoglycaemia and masks symptoms	Insulin-requiring diabetics
Vivid dreams, psychological symptoms	

Comparative trials confirm that all are equally effective if given in doses which produce equipotent beta-receptor blockade. The mechanism of action remains unknown, but is clearly not directly related to a reduction in cardiac output or depression of plasma renin activity, which were first speculated. Eleven beta-receptor antagonists are now available in Britain. What should determine the choice of any particular agent? Cardioselective beta-receptor antagonists are not cardiospecific, but their relative greater activity on the cardiac $beta_1$ receptors and lesser effect on the $beta_2$ receptors in the bronchi will confer a greater safety margin in patients with chronic airways disease. It must, however, be emphasized that all beta receptor antagonists can produce bronchospasm, and if possible should be avoided in susceptible patients. There is also a theoretical advantage in using a selective agent in diabetics requiring insulin, in whom recovery from hypoglycaemia depends upon $beta_2$ receptor stimulation of hepatic gluconeogenesis and hepatic and skeletal muscle glycogenolysis. In practice this may not be too important and the greater worry in diabetic patients is that all beta-receptor antagonists mask the warning symptoms of impending hypoglycaemia such as tachycardia, palpitations, anxiety and tremor.

The cardioselective agents are atenolol, acebutalol and metoprolol. Pharmacokinetic differences between agents may confer a clinical advantage. Atenolol, sotalol, acebutalol and nadolol are less quickly eliminated from the body, and it is clear that these can be effectively given as a once-daily treatment. Long-acting preparations of propranolol (Inderal L.A.) and oxprenolol (Slow Trasicor) have been developed, but there is some doubt about the absorption of the latter product (Petrie et al., 1980).

The usual effective dose range is less than was at first advocated. Few patients will have a worthwhile additional decrease in pressure when the dose of either propranolol or oxprenolol is increased to more than 320 mg a day. The dose–response curve for atenolol is flat above 100 mg daily (Marshall et al., 1979).

Practolol is no longer available for oral therapy because it produced an unpredicted syndrome of eye disease, skin rashes, sclerosing peritonitis and fibrosing pleurisy. No other beta-receptor blocking agent has been shown to produce a similar disastrous effect.

Alpha and beta adrenoceptor antagonist

Labetalol (Trandate) is a non-selective beta-receptor antagonist which possesses some alpha-receptor blocking activity ($\alpha : \beta = 1:7$). It is as effective as other beta-receptor antagonists in decreasing arterial pressure, but the alpha-receptor blockade produces postural hypotension in some patients. Parenteral administration is particularly effective in hypertensive crises and a titration infusion technique has been described by Brown and others (1977). The infusion is commenced at 20 mg for the 1st hour, 40 mg for the 2nd hour, 80 mg for the 3rd and 160 mg during the 4th hour.

Diuretics

Their mode of action is debated. The hypotensive effect may be to reduce peripheral resistance brought about by autoregulatory mechanisms in response to a persisting slight volume depletion resulting from natriuresis. Alternatively, diuretics may have a direct effect on the smooth muscle tone in the walls of resistance blood vessels, possibly mediated through prostaglandins.

Diuretics have a remarkably similar hypotensive potency. Thus the potent loop diuretics such as frusemide, do not have a greater therapeutic potential in hypertension than thiazides, and may not be as effective because of a short duration of action. Spironolactone, a relatively weak diuretic, is as effective as a thiazide (Roberts et al., 1979). The hypotensive effect is maximal at low doses so that, for instance, there is no additional effect produced by increasing the dose of bendrofluazide to more than 5 mg daily or chlorthalidone to more than 25 mg daily. There appears to be no benefit from combining different diuretics.

New diuretics have been developed and are marketed for treatment of hypertension. These include indapamide (Natrilix) and xipamide (Diurexan). They have no clear cut advantages over the thiazides. Gouty or hyperuricaemic hypertensive patients present a difficult problem and should not be treated with a diuretic because these agents cause hyperuricaemia and may provoke acute gout. Recently an ethacrynic acid derivative, tienilic acid, has been developed which is a diuretic but is unique in having an independent uricosuric activity. It decreases serum uric acid concentrations (Roberts et al., 1979). Unfortunately there is biochemical evidence that it causes hepatic damage and the clinical trials licence has been withdrawn.

The effect of a diuretic on potassium balance depends on its site of action within the nephron, that is to say proximally-acting diuretics increase potassium loss and distally-acting drugs such as direct antagonists of aldosterone (spironolactone) and those which block the exchange of sodium for potassium in the distal tubule (amiloride) will tend to cause potassium retention. With these agents there is a risk of hyperkalaemia. In general, potassium supplements are not routinely required when a thiazide is prescribed for hypertension. All the published data have been analysed by Morgan and Davidson (1980). However, serum potassium is wisely checked before anaesthesia and surgery to exclude hypokalaemia and the risk of hypokalaemia-induced cardiac arrhythmias secondary to hypocapnia during artificial ventilation.

The other major side-effects are listed in table III.

TABLE III. *Side-effects of diuretics*

Side-effect	Contraindicated in these patients
Potassium	
(a) Proximal acting (thiazides) $K^+\downarrow$	Watch for hypokalaemia, particularly in old people or those with a poor diet
Loop acting (frusemide, bumetanide) $K^+\downarrow$	
(b) Distal acting (spironolactone, amiloride) $K^+\uparrow$	Hyperkalaemia when renal function is reduced
Carbohydrate intolerance	Diabetics Watch for development of diabetes in others
Decreased uric acid excretion	Gouty or hyperuricaemic patients Watch for development of gout in others
Hyponatraemia	Particularly seen in elderly patients given too much diuretic Presents with nausea, anorexia, vomiting, confusion and drowsiness

Vasodilators

Hydrallazine, sodium nitroprusside, diazoxide and minoxidil are direct vasodilators. Prazosin acts as a vasodilator by blockade of the postsynaptic alpha-adrenoceptors. Hydrallazine and prazosin are commonly prescribed as long-term oral treatment. *Hydrallazine* (Apresoline), like other direct vasodilators, causes a reflex tachycardia which may be symptomatically troublesome. It is therefore best given to the patient who is already taking a beta-receptor antagonist. In slow acetylators, and particularly if the daily dose is greater than 150 mg daily, a systemic lupus erythematosus syndrome may develop. This presents with fever, arthralgia, lymphadenopathy and skin reactions (Bing et al., 1980).

Prazosin (Hypovase) has the advantage of having little or no effect on heart rate. Patients may faint after the first dose, and to overcome this important side-effect a low starting dose (0.5 mg) is recommended and it should be taken just before bedtime. Symptoms of postural hypotension continue to occur in some patients taking prazosin in the long term, but are not usually troublesome. The usual dose is 1–5 mg three times daily.

Minoxidil (Loniten) is a newly available potent agent. Its routine use is limited by sodium and fluid retention which may be severe, marked tachycardia, and hypertrichosis which is unacceptable to women. It is a drug to be used in patients with severe hypertension who are resistant to usual treatment (Dargie, Dollery and Daniels, 1977). It is usual to prescribe minoxidil with a beta-receptor antagonist and diuretic.

Diazoxide (Eudemine) has occasionally been used orally, but it produces unacceptable side-effects—severe fluid retention, diabetes, nausea and vomiting and hypertrichosis. It should be reserved for i.v. therapy.

Sodium nitroprusside (Nipride) is now available in a standard and stable solution. After injection it is converted to cyanide and then to thiocyanate in the liver. Thiocyanate has a renal clearance of 2.2 ml min^{-1} and accumulates in patients with renal failure. The vasodilator effect is attributable to the parent molecule. Sodium nitroprusside is nearly always successful in decreasing arterial pressure, but the rate of infusion must be adjusted meticulously. The initial rate is 0.5 $\mu\text{g kg}^{-1}\text{ min}^{-1}$. It has a short duration of action so the dose can be adjusted every 2 min until the arterial pressure is reduced to the desired value. The flow rate is then maintained and titrated against response. Long infusions should be avoided, particularly in patients with renal or hepatic insufficiency, because of the accumulation of thiocyanate.

Methyldopa

It is now known that methyldopa has an important site of action in the central nervous system. It is converted to methyldopamine and methylnoradrenaline by dopa decarboxylase in the brain. Methylnoradrenaline stimulates alpha-receptors in the brain stem and this causes a reduced outflow of sympathetic impulses and a decrease in arterial pressure.

The dose for most patients will be 500 mg once or twice a day. Larger doses often produce only a small additional effect, but cause more side-effects, the most troublesome of which are lethargy and an inability to concentrate. It can cause impotence. Sometimes patients develop a drug fever and an influenza-like illness, with malaise and joint pains, about 9–19 days after starting treatment. Symptoms rapidly improve when methyldopa is stopped. Hepatitis is a rare, but serious, complication of treatment and can be fatal. The Coombes test becomes positive in 20% of patients, but only 0.2% develop haemolytic anaemia. The onset of haemolysis may be acute or chronic and usually occurs within 18 months of starting treatment. Postural hypotension is occasionally troublesome.

Inhibitors of angiotensin I converting enzyme

Two compounds are being studied which are competitive inhibitors of the enzyme responsible for converting the largely inactive decapeptide, angiotensin I, to the vasoactive octapeptide angiotensin II. One is teprotide, which is of limited clinical use because it must be given i.v. The other is captopril, which is orally active and which has received considerable clinical attention. It reduces the plasma concentration of angiotensin II and therefore also of aldosterone. At the same time renin and angiotensin I concentrations (the components of the renin–angiotensin system proximal to the enzyme blockade) are increased. Its hypotensive action, however, may not be directly related to this effect and it is also thought to have effects on bradykinin and prostaglandin concentrations.

Captopril is effective in severe and resistant hypertension (Atkinson and Robertson, 1979). It is now available on prescription, and in some centres it has become the treatment of choice for refractory cases. Side-effects include rashes, pruritis and disturbance of taste. The most serious are membranous glomerulonephritis and agranulocytosis.

This is the first member of an exciting new group of drugs, and derived compounds may be produced which have lower toxicity.

ISCHAEMIC HEART DISEASE

Primary and secondary prevention

Many deaths attributed to ischaemic heart disease occur suddenly without any warning. Clearly it is better to prevent myocardial infarction than to treat the complications after the damage has been done. Infarction is usually associated with coronary atheroma and thrombosis. Current interest is centred on the role that lipid-decreasing agents, antithrombotic agents and the beta-adrenoceptor blockers play in prevention of ischaemic heart disease.

Lipids

Clofibrate (Atromid S) has been prescribed extensively in the past 15 years. The report of the Committee of Principal Investigators (1980) of the W.H.O. Cooperative Trial on Primary Prevention suggests that it should now only be used for certain specific lipid abnormalities and not for the routine reduction of cholesterol concentrations or for primary or secondary prevention. It produces unexpected and serious long-term side-effects. In this large European study there were 25% more deaths in the clofibrate-treated group than in a comparable high serum cholesterol control group.

The investigators had studied volunteers who were free of clinical ischaemic heart disease and who were classified into three groups according to the serum cholesterol concentration. Those in the upper third were randomly allocated to clofibrate or placebo therapy. The mean period of observation was 9.6 yr, 5.3 in the trial and 4.3 afterwards—a total of 150 000 man years. There were 157 deaths from ischaemic heart disease and 239 deaths from other causes in the clofibrate group compared with 138 and 179 in the control group. Diseases of the liver, gall bladder and intestines were significantly increased in those taking clofibrate.

The cause of the excess mortality is speculative. It continues after clofibrate has been stopped and it might be the result of a long-term toxic effect of clofibrate. It may be a consequence of reducing body cholesterol pools, and the implications of this trial on other methods of reducing cholesterol, such as dietary restrictions, are not yet clear.

Antithrombotic agents

The search for agents which could modify platelet behaviour began when it was recognized that platelets could have a key role in arterial thrombus formation. Three agents have been tested in clinical trials. These are aspirin, sulphinpyrazone and dipyridamole (Mitchell, 1980).

Aspirin irreversibly acetylates the platelet enzyme cyclo-oxygenase and so prevents the formation of thromboxane A_2, which aggregates platelets. It also reversibly inhibits the same enzyme in the vessel wall, thereby reducing production of the equally powerful anti-aggregatory, prostacyclin (PGI_2). The dose of aspirin which will produce a beneficial overall effect may be critical and currently it is suggested that this will be 300 mg (one tablet) every 1–3 days.

Four randomized controlled trials of aspirin treatment after myocardial infarction have been reported. The largest of these is the Aspirin Myocardial Infarction Study (AMIS). None has shown a statistical difference between aspirin and placebo (Elwood and Sweetnam, 1979). The evidence, however, is not yet conclusive because the studies hint at a possible benefit and further work is currently in progress.

Sulphinpyrazone (Anturan) was developed as a uricosuric agent, but was found to prolong platelet survival in man. It was thought that it might have anti-thrombotic activity and has been tested by The Anturan Reinfarction Trial Research Group (1980). The trial comprised 1558 patients, entered between 25 and 30 days after myocardial infarction. They were followed for an average of 16 months. Sulphinpyrazone was given in a dose of 200 mg four times a day and reduced sudden death during the first 7 months. There were 35 cardiac deaths in the placebo group and 17 in the sulphinpyrazone group. The difference appears to be in the frequency of sudden death and it is questioned whether, if effective, sulphinpyrazone had not an anti-thrombotic activity but an antiarrhythmic action. (Wilcox and coworkers (1980) have not been able to confirm an antiarrhythmic effect.) There is some weakness in the design of the trial and most physicians feel that it would be desirable for more work to be done to confirm the result before generally recommending sulphinpyrazone therapy to their patients.

Dipyridamole (Persantine) is a vasodilator known to be antithrombotic in animal studies and to inhibit platelet aggregation in man. In the Persantine–Aspirin Reinfarction Study (1980), 2026 patients were randomly allocated to three treatment groups. One group received dipyridamole 75 mg and aspirin 324 mg three times day, the second received the same dose of aspirin and placebo, and the third group received placebo only. Primary end-points were total mortality, coronary deaths and coronary frequency. The combination of dipyridamole and aspirin appears to have been beneficial, particularly in those patients who entered the study within 6 months of myocardial infarction.

Beta-adrenoceptor blocking agents

Enthusiasm for beta-receptor blockade in secondary prevention followed publication of the Multi-Centre International Study (1975). Practolol or placebo was given to 3038 patients on average 13 days after infarction, and the patients were followed up for 2 years. There were 47 cardiac deaths in patients taking practolol and 73 in those given placebo. Trials of alprenolol have also suggested that beta-receptor blockade may be effective in reducing death after myocardial infarction. However, no difference was found when propranolol was compared with placebo and it has to be concluded that the position at present remains confused.

Each clinician must make up his own mind on the basis of the existing evidence. I think none should be too ready to prescribe any of the drugs wholesale for primary or secondary prevention. History shows that premature acclaim for other interventions—like the anticoagulants, has led to disappointment.

ANGINA PECTORIS

Recognition of angina pectoris is all important. The symptoms can be overlooked or misinterpreted by both the patient and his doctors. The patient may dismiss his symptom as "indigestion" or he may deny chest pain, but if questioned admit that he gets chest "tightness—not pain" on exertion. The history is the most important means of making the diagnosis and the most important feature of it is that the patient experiences some discomfort when he exercises and this is rapidly relieved if he stops exercising. Difficulties in recognition can arise if angina occurs in an atypical site, such as the jaws or shoulder joints, and if it is precipitated more readily by emotion or cold temperatures.

The electrocardiogram is unhelpful because it will be normal unless the patient has had a previous myocardial infarction. Two investigations are now used to aid diagnosis. These are exercise testing and radionuclide imaging. The tests also help to distinguish the patient who does not have ischaemic heart disease. (This is often a middle-aged woman who complains of atypical chest pains, but who often firmly believes that her heart is at fault.)

Exercise testing. The patient exercises with gradually increasing workload on either a treadmill or a bicycle ergometer. The electrocardiogram is recorded throughout to monitor ST-segment changes. ST-segment depression of greater than 1 mm is considered to be a positive test (fig. 2). The test is generally safe, but should only be performed where full resuscitation facilities are available.

Radionuclide imaging. Two radiopharmaceuticals are routinely employed in departments of cardiology. These are thallium-201 and

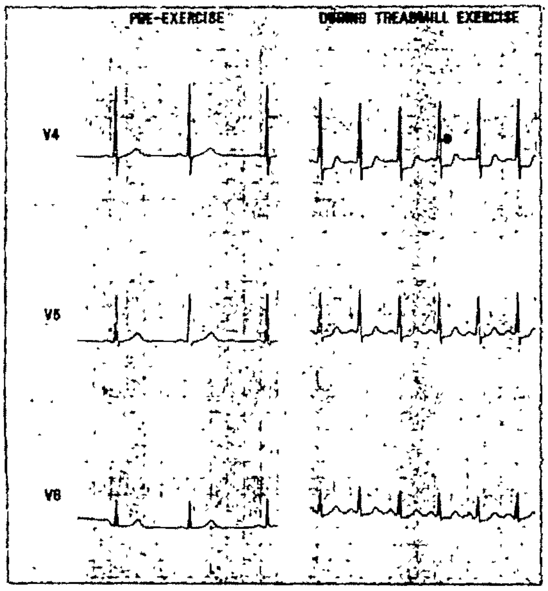

FIG. 2. Electrocardiograms recorded from a 48-yr-old man. Pre-exercise is normal, but during treadmill exercise he developed angina pectoris and the ST-segment is depressed flatly by 2 mm. This is a positive exercise test.

technetium-99 m. Thallium is a potassium analogue and is taken up by normally perfused myocardium. Areas of ischaemia are recognized by low uptake when the myocardium is scanned with a gamma camera. They are better defined if the heart is "stressed" by exercise or vasodilatation produced by dipyridamole before injection of thallium. Technetium-99 m is used to label the blood pool and ventricular wall motion may be studied either by a first-pass technique or by multi-gated imaging. Myocardial ischaemia is usually associated with detectable left ventricular dysfunction (Becker, 1980).

Angina without narrowing of the coronary arteries

Patients may present with angina without atheromatous narrowing of the coronary arteries. Important causes are aortic stenosis and hypertrophic obstructive cardiomyopathy (HOCM). Both should be detected on clinical examination. Patients with HOCM are treated either with beta-adrenoceptor blockade or verapamil.

Coronary artery spasm (Prinzmetal's variant angina)

In recent years it has been clearly shown that some patients with normal coronary arteries develop angina because of coronary artery spasm. This can only be firmly diagnosed with the demonstration of normal coronary arteries at arteriography and ischaemic electrocardiographic changes during episodes of pain. Chest pain is often troublesome at rest, but also occurs during exercise. It is typical of angina in quality and location and syncope may occur during an attack. The importance of diagnosis is that treatment with beta-receptor blockade is ineffective, whereas symptoms are relieved with vasodilator therapy—either long acting nitrates or nifedipine are recommended (Heupler, 1980).

Prognosis of angina

It is important to recognize that the diagnosis of angina need not be a life sentence. Quite apart from medical and surgical intervention, symptoms can resolve spontaneously. Duncan and colleagues (1976), diagnosed new and worsening angina in 251 men. They reviewed them 6 months later. Two hundred and twelve did not go on to have a heart attack and 66 of these were pain-free for the previous 3 months. These results are similar to those of other studies and emphasize the low risk of sudden death and possibility of spontaneous remission.

Management

Medicine v. surgery

The rapid development of aorto-coronary saphenous vein bypass surgery in the past decade has added a new perspective to the management of angina. Few now doubt that surgical treatment is the best way of completely relieving symptoms. Eighty per cent of patients treated surgically will be made either pain-free or much improved. Most will be able to resume their work and normal life (Westaby, Sapsford and Bentall, 1979). What are the risks of a surgical approach to angina? The mortality of coronary arteriography, an essential prerequisite for surgery, is 0.2% if the femoral approach is used. In the most successful centres the operative mortality is 2%. The risk increases if the left ventricular ejection fraction is reduced. There is also a 10% perioperative infarction rate and an unknown morbidity which includes chest wall infections and breakdown of the sites of removal of the saphenous vein.

Surgery is only palliative and does not attack the underlying disease process which continues to progress. There is a 5–10% annual recurrence rate of chest pain after the first year after operation and perhaps 20% of all grafts become blocked.

Does surgery prolong life? Present evidence suggests that the answer is yes if the left main stem is critically diseased or if there is important three-vessel disease. Five-year survival is not improved by operation if the patient has one or two-vessel disease (European Coronary Surgery Study Group, 1980). Surgery should be restricted to the proven indications of disabling chest pain, when full medical therapy has failed, and to the group of patients with extensive coronary artery disease and good left ventricular function in whom mortality is reduced by surgery.

Principles of management

General measures. The patient should stop smoking and increased arterial pressure should be treated. Patients with angina learn how to minimize attacks, but may benefit from advice about keeping warm and avoiding exercise after heavy meals.

Nitrates. These can be used prophylactically or for an acute attack. Glyceryl trinitrate paste applied to the skin is helpful for nocturnal angina.

Beta adrenoceptor blocking agents. Most patients who get angina more than occasionally, warrant treatment in addition to nitrates. Beta-receptor blockade is the mainstay of therapy.

Calcium antagonists. Not all patients respond adequately to beta-receptor antagonists; some patients develop side-effects and in others there are contraindications to the use of beta-receptor blockade, such as heart failure or asthma. The calcium antagonists are the major alternative form of treatment.

Beta-receptor antagonist plus a calcium antagonist. If inadequate relief is obtained from beta-receptor blockade then nifedipine, a calcium antagonist, can be safely given in addition. There is now objective evidence that the combination may be better than either drug alone (Lynch et al., 1980).

Consideration for *saphenous vein aorto–coronary bypass surgery*. As I have already outlined, patients who remain disabled despite an adequate trial of medical treatment should have a coronary arteriogram and left ventricular angiogram with a view to surgical treatment.

Unstable angina (Crescendo angina, preinfarction syndrome, acute coronary insufficiency or intermediate coronary syndrome)

There has been controversy about the acute management of unstable angina pectoris which is characterized by rapidly worsening angina, angina at rest and transient electrocardiographic changes during pain. Are patients best managed with emergency coronary bypass surgery or with intensive medical treatment? A prospective randomized trial has now been completed by the National Cooperative Study Group (1978). Of 278 patients entered, 90% had pain at rest in hospital and all had transient S-T segment or T-wave changes. The medically and surgically treated patients were comparable. The hospital mortality was 5% in the surgical group and 3% in the medical group. I conclude that it is best to give the patient intensive drug therapy with hospital bed rest. Drugs should include beta-receptor blocking agents, nitrates and analgesics. It can be expected that symptoms will settle in more than 80% of patients (de Feyter et al., 1979). Only if the patient fails to respond should a coronary arteriogram be performed. This investigation carries a higher risk during acute symptoms and the cardiac surgeon should be alerted and prepared to proceed to immediate surgery. The ability to provide intra-aortic counter pulsation with a balloon pump increases the safety margin.

Specific drugs

Nitrates

Nitrates dilate arteries and veins. The heart's preload is reduced because of pooling in the peripheral veins. This results in a decreased ventricular volume, decreased wall distension and therefore a reduced myocardial demand for oxygen. In addition to these effects there may be a benefit from increased myocardial blood flow. Vasodilatation has been demonstrated in the ischaemic zone in animal hearts. If coronary artery spasm is a factor in producing angina, nitrates would tend to relieve it.

Glyceryl trinitrate. A table absorbed sublingually acts within 2 min and can be used in an acute attack of angina or immediately before an activity which is likely to provoke angina. The tablets contain either 0.3 mg or 0.5 mg. The smaller dose may be less likely to produce the thumping headache which troubles many patients prescribed the more usual 0.5 mg. The other major side-effect is syncope as a result of venous pooling. Nitrates can be absorbed through the skin and a preparation of glyceryl trinitrate has been produced in the form of paste to be applied to the skin (it is not yet available on general prescription). Absorption is slow and the effect is prolonged. This is particularly helpful for patients troubled with nocturnal angina.

Reports on the efficacy of oral *long-acting nitrates* are controversial. One randomized double-blind study of nine patients showed that duration of exercise was prolonged for 3 h and there was less ST-segment depression for 2 h after oral isosorbide dinitrate (Sorbitrate, Isordil, Cedocard, Vascardin) when compared with placebo (Markis et al., 1979). Long-acting nitrates are more costly than glyceryl trinitrate, but are available as a chewable tablet which is an advantage for patients, often the elderly, who have dry mouths and have difficulty in dissolving the sublingual tablet.

Beta-adrenoceptor blocking agents

Beta blockade reduces the oxygen demand of the heart by reducing the heart rate · arterial pressure product and by depressing contractility.

The choice of which beta-receptor antagonist appears not to matter, except that long-acting agents like atenolol can be given effectively once daily. All are equally useful in treating angina pectoris (Thadani et al., 1980). Some patients fail to respond to this type of therapy and may benefit more from a calcium antagonist.

There are many case reports which suggest that there is a risk when acutely withdrawing beta-receptor blockade from the patient with ischaemic heart disease. It is suggested that severe angina, myocardial infarction, ventricular arrhythmias and even sudden death may occur in the days which follow stopping treatment. However, we have recently studied 20 patients with angina and proven severe three-vessel disease in whom we have acutely withdrawn atenolol treatment. We followed plasma concentrations of noradrenaline, heart rhythm with 24 h ambulatory monitoring and exercise performance with treadmill testing and multi-lead precordial mapping, over a period of 6 days. We found no evidence of sympathetic overactivity, rhythm disturbance or clinical deterioration.

Calcium antagonists

This group of agents includes nifedipine (Adalat), verapamil (Cordilox), perhexilene (Pexid), lidoflazine (Clinium) and prenylamine (Synadrin). All have unrelated pharmacological properties, but share a common ability to inhibit transmembrane calcium influx which is necessary for cardiac and smooth muscle contraction. The mode of action of prenylamine remains unclear, but the others appear to dilate both coronary and peripheral arteries. These agents are effective in the treatment of angina.

Nifedipine 10–20 mg three times daily can safely be given with a beta-blocking agent. Side-effects are caused by peripheral vasodilatation—headaches and flushing of the skin.

Verapamil also has potent anti-arrhythmic activity. It should not be given concurrently with beta-receptor blockade. This is because each drug inhibits A–V node function and there are risks of severe bradycardia and hypotension. Bala Subramanian and others (1980) have shown that verapamil 360 mg daily is effective in treating angina. In this controlled study there was significant improvement in ST-segment changes with multistage treadmill exercise.

Perhexilene has additional quinidine-like and mild diuretic properties. Side-effects are often troublesome and limit its use. These include a peripheral neuropathy, ataxia, increased intracranial pressure with papilloedema, liver disease resembling subacute alcoholic hepatitis and weight loss which can progress to cachexia.

Prenylamine 60–240 mg three times daily can cause skin flushing, headache and dizziness. Like lidoflazine (usual dose 360 mg daily), it may prolong the Q–T interval. Ventricular arrhythmias have been reported in patients with prolonged Q–T as a result of prenylamine therapy.

Heart failure and vasodilator therapy

I.v. vasodilators have been shown to improve the haemodynamic and clinical state of patients with severe heart failure complicating ischaemic heart disease. Prazosin, hydrallazine and sodium nitroprusside have been tried and acutely appear to be about equally effective. Unfortunately, most of the agents have been evaluated only during short-term administration. However, Colucci and others (1980) have now shown that long-term therapy with oral prazosin can result in significant functional and haemodynamic improvement in patients with severe congestive heart failure. In a randomized double-blind trial prazosin given in a dose of up to 16 mg daily produced improvement over a period of 2 months in treadmill exercise duration, echocardiographic ejection fraction and ejection fraction measured by radionuclide ventriculography.

Limitation of infarct size

Future developments of drug therapy for ischaemic heart disease will include intervention to limit the size of myocardial infarction, and lessen the chances of poor left ventricular function and heart failure. Infarct size can now be mapped electrocardiographically with multiple precordial leads; it can be imaged with radionuclides and monitored particularly with the release of the MB isomer of creatinine kinase.

To be successful, therapeutic measures will have to be taken within a few hours of the onset of pain. The most interesting result comes from the coronary care units in Oxford and Manchester (Yusuf et al., 1980). I.v. atenolol 5 mg was given at a median time of 4 h from onset of symptoms. It appears to decrease enzyme concentrations and enhance R-wave preservation. Fewer patients treated with atenolol compared with placebo-treated controls developed heart failure or cardiac arrest and death.

These preliminary results are encouraging and it is to be hoped that drug therapy will continue to improve the lot of the patient with ischaemic heart disease in the future.

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THE ROLE OF THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM IN CIRCULATORY CONTROL AND IN HYPERTENSION

E. D. MILLER

The normal arterial pressure is maintained by a complex interaction of neural and hormonal factors. When conditions arise which decrease arterial pressure, multiple systems are activated. The renin–angiotensin–aldosterone system is one such system with powerful vasoconstrictor capabilities. It is not surprising, then, that a derangement of this system may also cause hypertension. The following discussion will examine the role of the renin–angiotensin–aldosterone system in arterial pressure control with special emphasis for the anaesthetist. It should be remembered that other factors are also important, but because of extensive research in this area, it serves as a prototype for other systems that are either currently known (for example antidiuretic hormone) or are yet to be discovered.

HISTORY

In 1836, Richard Bright noted the correlation between the cardiovascular system and the kidney when he wrote "the hypertrophy of the heart seems in some degree, to have kept pace with the advance of disease in the kidneys." In the early 1900's several investigators attempted to produce alterations in arterial pressure by either altering renal blood flow or reducing renal mass, but most experiments were unrewarding. Goldblatt and others (1934) were the first to demonstrate persistent hypertension in dogs when a main renal artery was constricted by a clamp. From these experiments, investigators attempted to identify the substance released from the kidney which caused the hypertension. Tigerstedt and Bergmann (1898) had isolated the enzyme renin from the kidney, but it appeared to be chemically unlike the substance released from ischaemic kidneys. Working independently, two groups of investigators (Braun Menendez et al., 1939; Page and Helmer, 1939) both discovered the enzymatic nature of renin and isolated a substance which caused the hypertension, naming it hypertensin and angiotonin respectively. By mutual agreement, the substance was later renamed angiotensin. In 1954, Bumpus, Green and Page isolated a highly purified preparation of angiotensin. They were followed by Skeggs and colleagues (1954) who obtained pure angiotensin for the first time. Angiotensin was then synthesized by Bumpus, Schwarz and Page (1957), an event which set off an intense study of the chemistry of angiotensin.

With the knowledge made available by these investigators, the role of the renin–angiotensin–aldosterone system in normal and pathological states was then investigated. The literature in this area is extensive and, of necessity, only a few of the major contributors will be cited. So that the reader may understand how the renin–angiotensin–aldosterone system may control the circulation in normal and pathological states, a brief review of the renin cascade will be presented.

RENIN CASCADE

Renin is a highly specific proteolytic enzyme that is released from the kidney under a variety of stimuli. Renin granules are found in specialized cells on the afferent arteriole of the glomerulus. This specialized region of the arteriole is called the juxtaglomerular apparatus. Alterations in renin content of the kidney are made to occur by altering sodium intake. Such manoeuvres have been used to investigate the importance of the renin–angiotensin system in arterial pressure control. Recently, a purified preparation of dog renin has been isolated and antibodies to it have been produced (Dzau, Kopelman et al., 1980). Investigations which alter renin concentration or function will soon allow more precise definition of its importance.

Once released into the circulation, renin cleaves its substrate, an alpha-2-globulin synthesized by the liver, to produce the decapeptide angiotensin I. Angiotensin I is known to stimulate release of catecholamines from the adrenal medulla and to

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act on the central nervous system to increase systemic arterial pressure and induce thirst (Fitzsimmons, 1971; Solomon, Cavero and Buckley, 1974). However, most of angiotensin I is hydrolysed to angiotensin II, an octapeptide, by an enzyme located near the epithelial surface of the lung called "converting enzyme" (Oparil, Sanders and Haber, 1970). This rather nonspecific enzyme also is responsible for the breakdown of bradykinin. It is not known if converting enzyme activity is altered in disease states, but it would appear that an excess of this enzyme(s) is present and it is not the rate-limiting step in the formation of angiotensin II.

Angiotensin II has a variety of actions which are concerned with the regulation of arterial pressure and volume status of the individual. Angiotensin II is a potent vasoconstrictor having a direct effect on arteriolar smooth muscle. Beside this effect, however, it also produces a positive inotropic effect on the heart, stimulates and potentiates the release of catecholamines and may enter or be formed within the central nervous system to help regulate arterial pressure (Ganten, Hutchinson and Schelling, 1975). These effects of angiotensin II are short-lived with a half-life of the peptide measured in seconds. Angiotensin II is inactivated in the plasma by angiotensinase and the liver is also an important site for clearance. Decreased liver blood flow has been shown to prolong the effects of renin (Johnson et al., 1971).

While angiotensin II continues to be present in the circulation, aldosterone biosynthesis by the adrenal gland is begun and it is released into the circulation. It was originally thought that ACTH was the most potent stimulus to aldosterone secretion, but more recent evidence suggests that angiotensin II is the more potent (Davis, 1975). The effect of aldosterone on the kidney is to reabsorb sodium and with it water, at the expense of potassium. This additional sodium and water, which is retained, results in changes in extracellular fluid volume with a resultant increase in effective blood volume.

Renin substrate or angiotensinogen concentration remains constant and normally is not the rate-limiting step in the renin cascade. However, in patients taking oral contraceptives, angiotensinogen increases three- to five-fold. Laragh and colleagues (1967) have suggested that this increase in substrate leads to an increased rate of generation of angiotensin II within the body. Crane, Harris and Winsor (1971) have shown that women who become hypertensive shortly after beginning oral contraceptives will normalize their arterial pressures if the oral contraceptives are discontinued. Certainly, all women do not become hypertensive with oral contraceptives, but the frequency may be as great as 15% (Tyson, 1968).

This is the classic view of the renin–angiotensin–aldosterone system. However, more recent work suggests that other peptide fragments of the renin cascade can be active. Goodfriend and Peach (1975) have described angiotensin III which is a seven amino acid peptide. This peptide appears to be equally as important as angiotensin II in aldosterone control, but without its full pressor properties. Angiotensin III when administered into the central nervous system has also been shown to decrease renin release while causing an increase of arterial pressure. Future work will determine the importance of these peptide fragments on arterial pressure and volume states of the individual (Peach, 1977).

Before a discussion of the role of the renin–angiotensin–aldosterone system in circulatory homeostasis, two important advances in the field must be described: the measurement of plasma renin activity and the development of inhibitors of the renin–angiotensin system. Without these two advances, an appreciation of this important group of peptides would not be possible.

Measurement of renin activity

The initial measurements of renin or angiotensin relied on the pressor response which occurred when specially prepared serum from the experimental animal was injected into an unanaesthetized trained dog. A dog unit of renin or of angiotensin, usually called a "Goldblatt unit" was defined as that quality of renin (angiotensin) which induced a maximum increase of 30 mm Hg, of the direct, mean, systemic arterial pressure, in about 2 min after the completion of the injection (Goldblatt et al., 1943). Few laboratories were able to sustain such a colony of dogs and therefore few laboratories measured renin activity. Boucher and colleagues (1964) modified the technique and injected serum extracts into nephrectomized rats. This allowed more laboratories to measure renin activity, but comparison of results between laboratories was at best difficult and only a small number of samples could be examined.

A dramatic advance in the measurement of renin activity was achieved by Haber and colleagues (1969) when the radioimmunoassay technique was used to measure plasma renin activity. Briefly, assay conditions are set so that the renin present in the sample, can generate angiotensin I. Conversion of angiotensin I to angiotensin II is prevented by the addition of inhibitors to the plasma. A duplicate plasma sample is also prepared, but is kept cold so that the renin is unable to carry on its enzymatic activity. Radioactive angiotensin I and antibody to angiotensin I are added and the mixture allowed to incubate. The separation of bound from free antigen is accomplished by differential adsorption of the free material onto activated charcoal and the concentration of the antibody-bound antigen in the supernatant is determined by gamma counting. The more radioactive angiotensin I present, the lower the renin activity which produces competing unlabelled angiotensin I. By this technique, the plasma renin activity (PRA) is determined and reported as nanograms of angiotensin I generated per hour per millilitre of plasma. PRA for 16 healthy volunteers on a sodium diet of 110 mmol in the supine position was $1.02 \pm 0.21\,\mathrm{ng\,ml^{-1}\,h^{-1}}$ (Haber et al., 1969). The development of this assay and its subsequent modifications have allowed mass screening of hypertensive patients as well as permitting different laboratories to compare their results.

Inhibitors of the renin–angiotensin system

Two clinically useful classes of specific inhibitors of the renin–angiotensin system have been angiotensin II antagonists and competitive inhibitors of converting enzyme. These inhibitors were developed knowing the chemistry of the renin–angiotensin system, which had been well established in the 1950's and 1960's.

The best studied angiotensin II antagonist is saralasin or sar-1-ala-8-angiotensin II. This compound was selected for extensive testing because it seemed to have less agonistic effect on vascular smooth muscle than other competitive antagonists of angiotensin II. Saralasin blocks the pressor response to exogenous renin, angiotensin I and angiotensin II in a dose-dependent fashion in intact animals (Pals, Masucci and Denning, 1971). Saralasin has been shown to prevent or reverse the binding of labelled angiotensin II to high affinity sites in adrenal cortical tissue homogenates and to inhibit aldosterone production in the intact animal (Johnson and Davis, 1973; Glossman, Baukal and Catt, 1974). The half-life of saralasin is 4–5 min compared with 15 s for angiotensin II (Pettinger, Keeton and Tonaha, 1975). One disturbing feature of this peptide is its agonist properties when it is initially infused (Dunn et al., 1976). This, as well as the fact that the peptide can only be given i.v., has halted any effort to market saralasin as either a diagnostic drug or therapeutic drug for the treatment of hypertension. It still remains an important tool for research on the physiological role of angiotensin II.

At the same time that competitive inhibitors of angiotensin II were being synthesized, Ferreira (1965) discovered a bradykinin-potentiating factor present in the venom of the *Bothrops jararaca* snake. Shortly thereafter Ondetti and others (1971) elucidated the structure of the peptides present in the venom and showed that one could inhibit converting enzyme activity. Further work on peptides that could inhibit converting enzyme showed that a nonapeptide with several proline substitutions would be the most active, and this substance was designated SQ20881 and named teprotide. This compound was attractive because it could block the conversion of angiotensin I (which has limited pressor properties) to angiotensin II. It also appeared that bradykinin blood concentrations were not increased at the drug concentrations necessary for inhibition of angiotensin conversion. However, teprotide is a straight-chained peptide that must be given i.v., thereby limiting its therapeutic usefulness.

In 1977, Ondetti, Rubin and Cushman (1977) synthesized an orally active agent, captopril (SQ14 225) which competitively inhibited angiotensin-converting enzyme without acting as a substrate. While the mode of action was at first thought to be solely through inhibition of converting enzyme, the long-term effects of this drug in man appear to be more complicated (Laragh et al., 1980). Studies in progress will define more precisely the role of this drug in the inhibition of the renin–angiotensin system.

In summary, the renin–angiotensin–aldosterone system is comprised of a series of peptides (except for aldosterone—a steroid) which have specific properties directed toward arterial pressure and volume control in the organism. An index of the activity of renin can now be estimated through the use of radioimmunoassay. Inhibitors of the renin–angiotensin system have been synthesized so that we can not only measure plasma renin activity, but also obtain some indices of the importance of angiotensin II in arterial pressure control in normal and pathological states.

FACTORS CONTROLLING RENIN RELEASE

For the potent peptide angiotensin II to be formed, renin must be released from the juxtaglomerular cells of the kidney. The stimuli responsible for the release of renin are complex and have recently been reviewed (Davis and Freeman, 1976). It is now clear that, in many situations, the rate of renin release is altered by simultaneous changes in several variables which act through one or more of three groups of mechanisms. The three mechanisms are: (1) two intrarenal receptors, the renal baroreceptor and the macula densa, (2) the renal nerves and an adrenergic receptor in the kidney, and (3) a number of humoral agents including adrenaline and noradrenaline, sodium and potassium ions, angiotensin II and antidiuretic hormone, oestrogens and adrenal steroids.

It has been known since the work of Tobian, Tomboubian and Janacek (1959) that changes in renal perfusion pressure altered renin release. With decreased perfusion pressure, renin was released despite normal renal blood flow (Gutmann et al., 1973). The release of renin was rapid with renal artery constriction and gave credence to the belief that the renin–angiotensin system was able to respond rapidly to changes in arterial pressure within the individual. Another intrarenal mechanism for the release of renin is also present. The macula densa of the distal convoluted tubule is in close proximity to the juxtaglomerular apparatus and senses renal tubular fluid concentration in the distal tubule. With decreased sodium delivery to the tubule, as would occur during a low sodium intake, renin is released. This occurs without a change in perfusion pressure to the kidney. Both of these mechanisms are operative and are thought to fine-tune the individual's arterial pressure to changes in sodium intake and resting arterial pressure.

The juxtaglomerular apparatus is also richly innervated by sympathetic nerves. Either when sympathetic nerves are stimulated or when catecholamines are infused into the kidney, renin is released (Johnson, Davis and Wiltz, 1971). In man it is known that manoeuvres such as assumption of the upright posture, tilting, exercise and exposure to cold stimulate the renal nerves and increase renin secretion. It appears that many of these responses may be blocked by beta-adrenoceptor blocking drugs (Assaykeen, 1972).

The third mechanism responsible for the release of renin is hormonal. Many of the hormones exert a negative feedback on renin release. DeChamplain and colleagues (1966) reported that nonpressor quantities of angiotensin II infused systemically suppressed plasma renin activity in man. Shade and others (1973) have shown that the infusion of antidiuretic hormone is able to decrease renin release. The mechanism responsible appears to be a direct effect of this peptide on the juxtaglomerular cells.

These various mechanisms which cause or inhibit the release of renin are operative in the patient who is scheduled for anaesthesia and surgery. How the release of renin will affect the arterial pressure and volume status of such surgical patients will be the focus of the following discussion.

NORMOTENSIVE PATIENTS

The renin–angiotensin–aldosterone system plays little role in the maintenance of normal arterial pressure in the sodium-replete, supine subject (Collier, Robinson and Vane, 1973). However, when sodium depletion occurs, the maintenance of arterial pressure is more dependent on the renin–angiotensin system. Thus, if an inhibitor of the renin angiotensin system is infused in sodium-depleted patients, arterial pressure decreases with little increase in heart rate.

More dramatic evidence for the role of the renin–angiotensin system is noted in subjects who are sodium-depleted and then placed on a tilt table. The normal response to tilting is for plasma renin activity and plasma aldosterone activity to increase markedly. Haber and colleagues (1975) showed that, if such subjects were treated with a converting enzyme inhibitor and then tilted, arterial pressure decreased from 106/69 to 65/22 mm Hg and 12 of the 13 subjects fainted. The autonomic nervous system was unable to compensate when the renin–angiotensin system was so inhibited.

The renin–angiotensin–aldosterone system is also important whenever haemorrhage occurs. Scornik and Paladini (1964) first showed that angiotensin was increased after haemorrhage in man. With severe haemorrhage, the renin–angiotensin system is important in maintaining arterial pressure in either unanaesthetized or anaesthetized animals (Miller, Longnecker and Peach, 1979). Inhibitors of the renin–angiotensin system with possible therapeutic implications have been used in haemorrhage. Errington, Rocha and Silva (1974) and Morton and colleagues (1977) showed that irreversible shock could be prevented if inhibitors of the renin–angiotensin system were infused before haemorrhage. Whether improved survival in patients with haemorrhagic shock can be achieved by using such inhibitors in man has not been demonstrated.

One area of clinical medicine in which inhibitors of the renin–angiotensin system have been used in normotensive man is in patients with congestive heart failure. Watkins and colleagues (1975) and others had shown that, in experimental forms of congestive heart failure, there was an initial increase in plasma renin activity and aldosterone. Once fluid retention had occurred, plasma renin activity returned to control, suggesting that activation of the renin–angiotensin system was an important step in the initiation of congestive heart failure. Dzau, Colucci and colleagues (1980) treated eight patients in severe congestive heart failure with captopril and found a dramatic improvement. There are presently many centres evaluating the effectiveness of this drug for patients with congestive heart failure.

During anaesthesia and surgery, increased plasma renin activity has been reported. However, when stable states of anaesthesia are examined, plasma renin activity is not increased (Robertson and Michelakis, 1972; Miller, Ackerly and Peach, 1978; Miller, Longnecker and Peach, 1978). Interestingly, inhibition of the renin–angiotensin system causes a decrease in mean arterial pressure in rats anaesthetized with halothane and enflurane, but not in animals anaesthetized with ketamine or fluroxene. Since converting enzyme activity is not altered by anaesthetics, the apparent disparity between a decrease in arterial pressure and unchanged plasma renin activity remains unexplained (Miller et al., 1979; Knight et al., 1980).

As in the awake state, during anaesthesia the renin–angiotensin system assumes a greater role in arterial pressure support in hypovolaemia or in sodium-depleted animals (Miller, Ackerly and Peach, 1978). With surgery, the increases in plasma renin activity are even greater and are a main contributor in arterial pressure support as well as aldosterone secretion (Bailey et al., 1975; Taylor et al., 1977). The dramatic increase seen in aldosterone plasma concentrations in patients undergoing cardiopulmonary bypass correlates with the loss of potassium seen in the urine of these patients. It is one explanation for the necessity of potassium replacement in the period after operation.

The use of sodium nitroprusside to decrease arterial pressure during operation causes an increase in plasma renin activity (Khambatta, Stone and Khan, 1979). That this increase in plasma renin activity is important in arterial pressure control has been demonstrated through the use of saralasin (Miller et al., 1977). The suggestion by Khambatta's group (1979) that the rebound hypertension seen once sodium nitroprusside was discontinued was a result of renin release has been confirmed. When animals pretreated with saralasin were given sodium nitroprusside to decrease arterial pressure, the discontinuation of SNP did not result in rebound hypertension in animals so treated (Delaney and Miller, 1980). This may have important therapeutic implications in a small group of patients, such as those undergoing intracranial surgery.

In summary, the renin–angiotensin–aldosterone system is an important control mechanism for the arterial pressure and volume status of the individual. Anaesthetic agents do not appear to alter the ability of this system to exert control. The system is able to compensate for acute changes in sympathetic tone and vascular volume in an attempt to restore the individual to a "normal" status. However, it is possible for this system to become unbalanced, and in some circumstances, this derangement has been shown to lead to hypertension.

HYPERTENSIVE PATIENTS

Because angiotensin II is such a potent vasoconstrictor and because aldosterone causes sodium retention, much effort has been spent on defining the role of the renin–angiotensin–aldosterone system in various forms of hypertension. By necessity, only a very few of the studies which have examined this complicated field of study can be addressed.

Since Goldblatt's early work, investigators knew that partial obstruction of the renal artery would cause hypertension. However, as the measurement of plasma renin activity became available, it was found that some patients with renovascular hypertension had normal plasma renin activity. This aberrant finding was explained when various inhibitors of the renin–angiotensin system were infused (Miller et al., 1972; Gavras et al., 1973). These workers found that the initiation of renovascular hypertension was a result of renin release, but that after aldosterone caused an increase in effective blood volume, plasma renin activity would decline. The hypertension persisted, however, because of the increased blood volume and a probable resetting of the baroreceptors. Some centres have used inhibitors of the renin–angiotensin system in a prognostic test in patients with renovascular hypertension (Streeten et al., 1975). It would appear that patients who are unsuitable surgical candidates may well benefit from specific inhibitors of the renin–angiotensin system. Anaesthetic management of such patients is not unlike that of other hypertensive patients (Prys-Roberts, 1979).

Another derangement of this system is primary aldosteronism (Conn, 1955). When this syndrome was first described, some believed a large number of patients with hypertension would be found to exhibit aldosterone excess. With improved assay techniques for renin and aldosterone, this belief became untenable. Primary aldosteronism is a rare disease caused by an adenoma which produces aldosterone. The patient presents with hypertension, hypokalaemia, low plasma renin activity and metabolic alkalosis. Surgery to remove the adenoma results in an 80–90% cure of hypertension. There are few anaesthetic reports (Gangat et al., 1976), but my personal experience demonstrates these patients to be no more difficult to manage than other hypertensive patients once potassium replacement has been accomplished.

By far the majority of hypertensive patients have no known identifiable cause for their hypertension. Page and McCubbin (1968) proposed the mosaic theory of hypertension which attempts to link several factors together. Certainly factors of heredity, salt intake, psychological influences and the sympathetic nervous system are all thought to be important. The bulk of research and drug therapy has been aimed at the sympathetic nervous system, but it now appears that the renin–angiotensin system may also be important in either initiating or contributing to the increased arterial pressure in patients with essential hypertension.

The role of the renin–angiotensin system in essential hypertension is most complex. Helmer (1964) showed that about 25% of patients with apparent essential hypertension had low renin concentrations. Since then, numerous reports have classified patients according to their plasma renin activity. The fact that subsets of patients with essential hypertension existed suggested interesting diagnostic and therapeutic possibilities. Subsequently, Brunner and colleagues (1972) demonstrated that patients with low renin hypertension were at much less risk of vascular complications and that diuretic therapy was very effective for control of their hypertension.

These data were hotly debated and numerous reports have since appeared. Doyle and colleagues (1973), Genest and colleagues (1973) and Mroczek, Finnerty and Catt (1973) have all examined this question. They, like Brunner, found a group of low renin hypertensive patients, approximately 30% of the total. However, they could not find a decreased frequency of vascular complications. Doyle felt that Brunner's observations of risk could be explained by the slightly lower arterial pressure found in the low-renin hypertensives compared with high-renin hypertensives who comprise about 15% of all hypertensive subjects. Although this issue is still being debated, it appears now that the measurement of plasma renin activity in patients has little therapeutic or prognostic implication. This does not rule out the importance of the renin–angiotensin system in hypertension. Further evidence in support of a role for the renin–angiotensin system was presented when captopril, the converting enzyme inhibitor, was administered to patients with essential hypertension. Arterial pressure decreased in all patients. There was no significant correlation between pretreatment plasma renin activity and the degree of arterial pressure decrease (Gavras et al., 1978). Since other explanations for the decrease in arterial pressure were not found, it is thought that the inhibition of the renin–angiotensin–aldosterone system may interact with unknown control mechanisms to help decrease arterial pressure in patients with essential hypertension. Whether the drug acts through central nervous system mechanisms or acts to inhibit angiotensin II production at some site in the vascular smooth muscle is unknown. Such observations as these tantalize investigators studying how the renin–angiotensin system may be involved in essential hypertension.

SUMMARY

The control of arterial pressure in normal and pathological states is governed by many mechanisms. The renin–angiotensin–aldosterone system is one mechanism which may be activated. The formation of the potent vasoconstrictor angiotensin II and the synthesis of aldosterone provide a means of arterial pressure regulation. With the recent introduction of specific agents which block the renin–angiotensin system, new appreciation of the role of this system is being formed. It is premature to predict whether we, as anaesthetists, will use such agents in our anaesthetic practice. However, we will see some patients who present for surgery taking such medication. How this will influence the patient's response to surgery is unknown. Inhibition of the renin–angiotensin system may allow better perfusion of vital organs. It may, however, be detrimental to the patient who needs this defense mechanism for support of his arterial pressure. At the present time these are all unsettled questions. Through the use of specific inhibitors of the renin–angiotensin system its importance will be defined, much as alpha- and beta-adrenoceptor antagonists have clarified our understanding of the sympathetic nervous system.

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SPECIAL ULTRASONIC METHODS FOR THE ASSESSMENT AND IMAGING OF SYSTEMIC ARTERIAL DISEASE

J. P. WOODCOCK

Ultrasonic investigation now plays an important role in the diagnosis of extracranial carotid disease and in the diagnosis of occlusive arterial disease of the lower limb. Although blood vessels were visualized ultrasonically as early as 1957 (Howry, 1957), it is only since the development of Doppler ultrasound techniques that any major advance has been made in the diagnosis and management of patients with systemic arterial disease. The major applications of Doppler ultrasound are based on the study of blood flow and it is necesary to describe the type of equipment now available in order to appreciate the clinical information obtainable.

METHODS

There are basically four types of ultrasound instrumentation used to investigate the arterial system, namely the B-scanner, Doppler flowmeter, Duplex scanner and the Doppler scanner.

B-scanner

The orthodox ultrasonic B-scanner as used in obstetrics, for example, is a brightness-modulated, two-dimensional display of anatomical structures within the body. The direction and position of the time-base across the display is linked to the direction and position of the ultrasonic beam across the patient, as illustrated in figure 1. If the probe is scanned over the patient and the information stored, then a two-dimensional picture is built up. Real-time B-scanners are now available in which the display is produced by either an electronic or a mechanical sweeping of the ultrasonic beam. This produces a flicker-free display in which moving structures can be seen.

Doppler flowmeter

When an ultrasonic wave is reflected or scattered by a moving object, the signal returning to the receiving transducer is shifted in frequency. If the ultrasound beam is inclined at an angle θ to the direction of flow of blood, then the Doppler shift frequency Δf is given by:

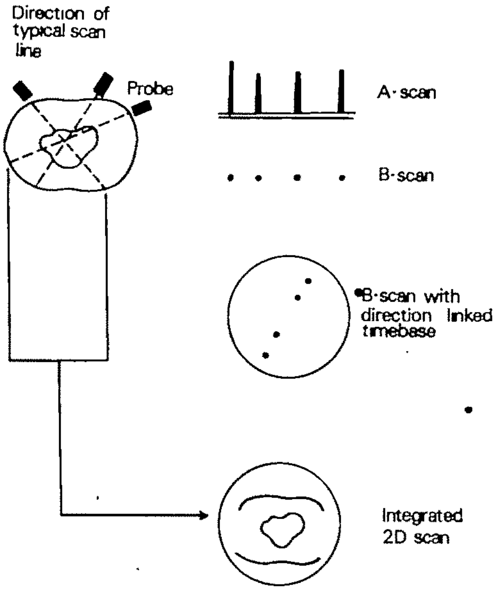
Direction of typical scan line
Probe
A-scan
B-scan
B-scan with direction linked timebase
Integrated 2D scan

FIG. 1. Principle of operation of the ultrasonic B-scanner.

$$\Delta f = \frac{2fv\cos\theta}{c}$$

where f is the transmitted frequency, c is the velocity of sound in blood and v the speed of the blood. It can be seen that the Doppler shift, for a given transmitted frequency, is proportional to the velocity of the blood, and the angle of inclination θ.

The basic Doppler instrument is a continuous wave device, which means the emitting transducer is continuously excited. The scattered wave is received by a second transducer and the instantaneous frequency difference between the emitted and received waves is measured. This Doppler-shift frequency varies both in time, over the cardiac cycle, and in position, across the lumen of the blood vessel. With a continuous wave system, information can be gained about the variation of

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blood velocity over the cardiac cycle in a blood vessel which intersects the ultrasonic beam from the transmitter. No depth information is available. The received signal contains a spectrum of Doppler-shifted signals because of the existence of a velocity profile across the vessel lumen. These received signals can be processed in a number of ways to produce information about flow direction (Coghlan and Taylor, 1976).

In the range-gated instruments a single transducer acts as emitter and receiver, and during the interval between successive pulses the transducer receives the scattered signal from the moving blood cells. Signals from different depths are received at different times and, by means of a gated receiver, the instrument can accept signals from any point across the vessel lumen.

Duplex scanners

Duplex scanners are a combination of real-time B-scanner and a direction-resolving, pulsed, ranged-gated Doppler flowmeter. Instruments such as these produce a real-time B-scan image of the area of interest, and the sample volume of the Doppler flowmeter can be placed at a particular point of interest within the vessel lumen.

A typical system operates at 5 MHz and consists of three transducers mounted on a wheel which rotates continuously, sweeping out a new image frame at a rate of 30 per second. The image can be stored, and one of the transducers used as a gated pulsed Doppler transducer to sample the blood velocity at a particular point in the vessel. The position of the Doppler beam is indicated by a white line on the display screen, and the position of the sample volume is shown as a white spot on this line. The position of the sample volume and the direction of the Doppler ultrasound beam are adjusted using an arm connected by means of a servomechanism to the transducer. A block diagram of the system is shown in figure 2.

Doppler scanners

The simplest Doppler imaging system consists of a continuous-wave Doppler flow detector, a storage monitor to display the image, and a probe position resolver. The position resolver is mechanically linked to the doppler probe and delivers signals to the storage monitor. When a Doppler shift signal is detected, a bright spot, corresponding to the probe position, is stored on the monitor. As the probe is moved over the skin overlying the blood vessel an image of the projection of the blood vessel on the skin surface is generated on the screen. The limitation of this simple continuous wave system is that only one projection can be obtained. In order to study the three-dimensional flow image it is necessary to pulse the transmitted ultrasonic signal, and time-gate the received signal.

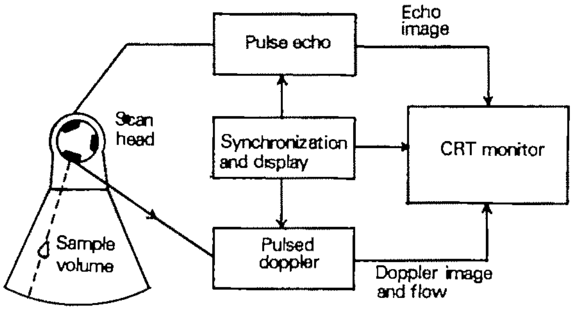

FIG. 2. Block diagram of the Duplex system.

Pulsed Doppler imaging systems require a position resolver which combines the probe position signals, and the signals corresponding to the position of the detected flow point in front of the transducer. It is then possible to produce images in three orthogonal planes of the internal lumen of the blood vessel. A block diagram of a multichannel Doppler imaging system is shown in figure 3. Three orthogonal projections of the Doppler image of a carotid artery bifurcation are shown in figure 4.

CLINICAL APPLICATIONS

The major clinical applications of ultrasound to the systemic arterial system are in the investigation of the extracranial carotid arteries and in the arteries of the lower limb. The information available from ultrasonic techniques lies in the appearance of the blood vessels on the real-time B-scan, Doppler image in three dimensions, and in the variation of the doppler-shift signal over the cardiac cycle. This information will be discussed in detail with a view to determining the best approach to the non-invasive diagnosis of systemic arterial disease.

Investigation of carotid artery disease

Clinically useful information can be gained from the carotid arteries using the real-time and Doppler imaging systems, and also by investigating the variation in blood-velocity over the cardiac cycle, and a combination of these techniques will

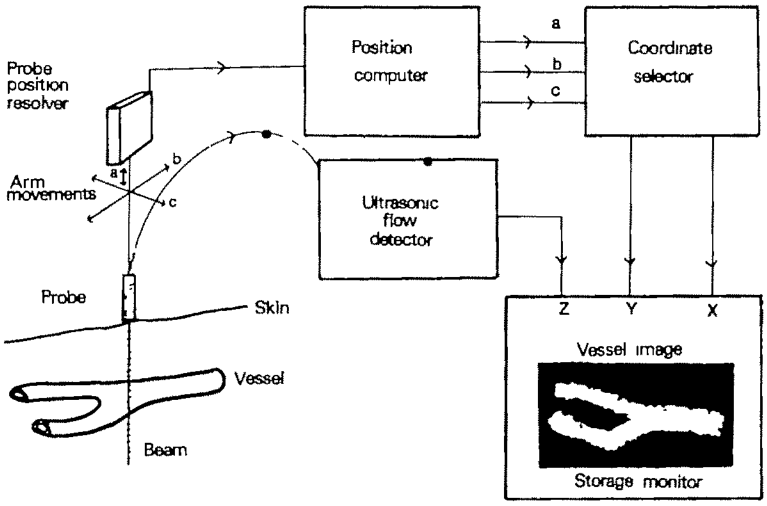

FIG. 3. Principle of operation of a multi-channel Doppler imaging system.

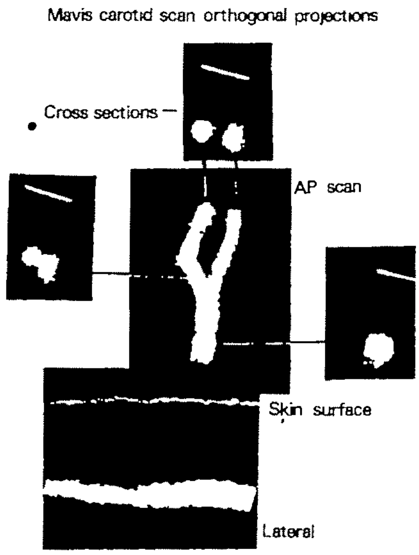

FIG. 4. Three-dimensional Doppler images of a carotid bifurcation.

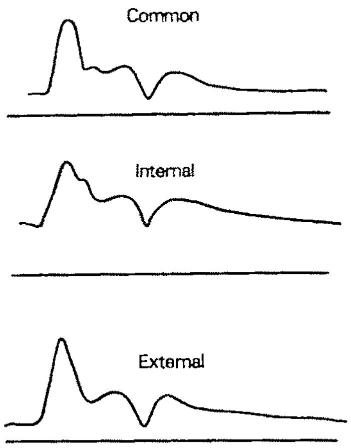

FIG. 5. Maximum blood-velocity/time waveforms recorded from the common, internal and external carotid arteries.

be shown to be the most sensitive in the detection of arterial disease.

Blood-velocity/time waveform over the cardiac cycle

Typical maximum blood-velocity/time waveforms from the common, internal and external carotid arteries are shown in figure 5. It can be seen that there is a relatively higher diastolic flow component in the internal carotid. Baskett and colleagues (1977) investigated a number of features of these waveforms and found that the most consistent parameter which demonstrates change with age and disease is the ratio of the two peaks in systole, A/B. From a total of 800 asymptomatic volunteers aged from 5 to 90 years, the ratio A/B decreased with age until the 6th decade, after which it remains at the value of approximately 1.2. Baskett measured the A/B ratios at both the common carotid artery and the supraorbital artery. These two values of A/B, shown in figure 6, one from each artery, were plotted on a graph. Their results show that, if the A/B ratio in either vessel is less than 1.05, then there is an 88% probability of disease at the carotid bifurcation. When the A/B ratio in both vessels is greater than 1.05, then there is an 80% probability of a normal bifurcation.

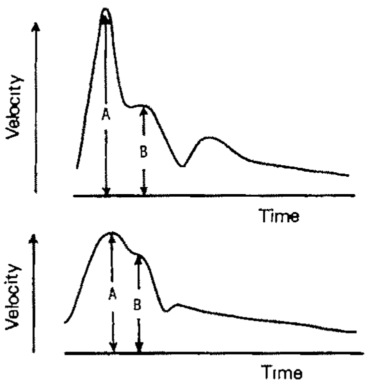

FIG. 6. A/B ratio in the detection of carotid stenosis.

Reinertson and Barnes (1976) showed that, in order to detect accurately changes in blood-velocity produced by minor stenoses, it is important to investigate the whole Doppler-shift spectrum, and not just the maximum frequency envelope used to calculate the A/B ratio.

The normal Doppler spectrum of the internal carotid artery shows that the greatest signal amplitude is associated with the maximum frequency envelope, as illustrated in figure 7A. Distal to stenoses which reduce the lumen by 25–50%, the spectrum during systole exhibits increasing amplitudes in the lower frequency range, as shown in figure 7B. This is referred to as spectral broadening. Blackshear and colleagues (1979) examined spectral broadening and showed that 66% of vessels with angiographically demonstrable mild irregularity of the wall had minimal spectral broadening. In the range of 10–49% diameter stenosis, 78% exhibited spectral broadening while all of the high-grade stenoses were positive.

It is clear from the above discussion that there are difficulties in the assessment of carotid artery disease using waveform shape data alone. However, further information can be gained, particularly concerning the internal carotid artery, from periorbital Doppler signals. These investigations in the vicinity of the orbit attempt to determine flow direction—whether flow in the supraorbital or frontal artery is into or out of the orbit—and to study changes in flow direction during manual compression of the supply arteries. The distal internal carotid artery becomes the ophthalmic

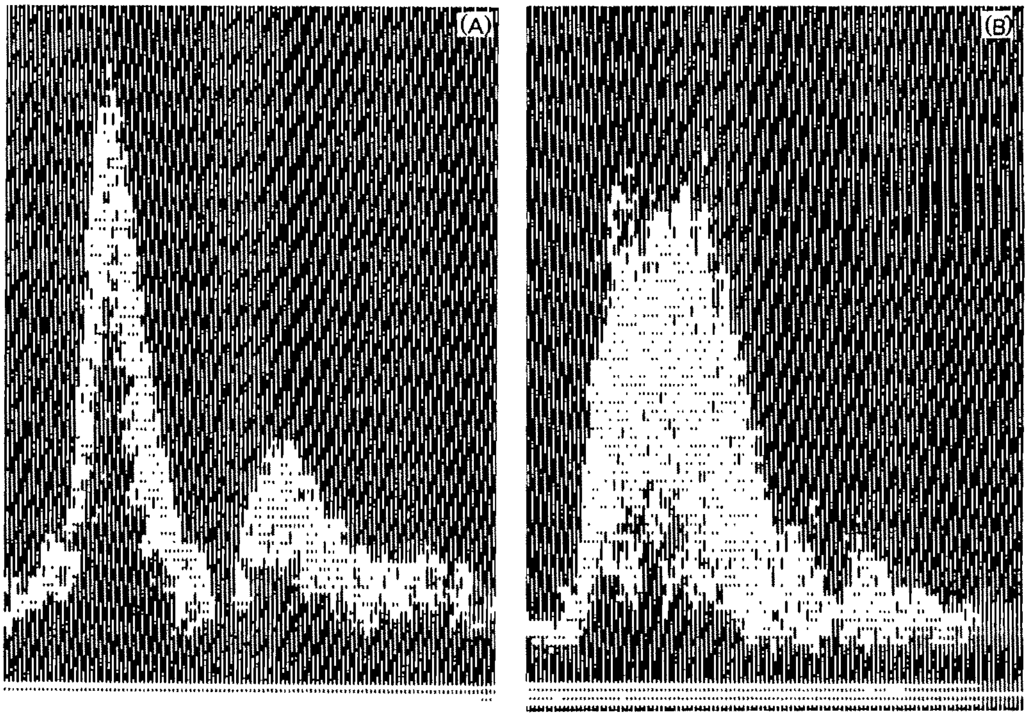

FIG. 7. Spectral broadening in (A) normal internal carotid and (B) distal to a 30% diameter stenosis of the internal carotid.

artery, which then branches to form the supraorbital and the frontal arteries. Both of these anastomose with terminal branches of the external carotid artery in more than 90% of the population. Brockenborough (1969) showed that, if flow is monitored over one of these terminal branches of the internal carotid, manual compression of the ipsilateral superficial temporal artery produces an enhanced signal in a direction out of the orbit, in the normal circulation. If the pressure in the internal carotid is reduced because of occlusive disease, then flow may occur from the external carotid via the collateral circulation to the supraorbital and frontal arteries. In this situation flow will be into the orbit and manual compression of the ipsilateral temporal artery reduces flow into the orbit. This type of examination is known as the temporal artery occlusion test (TAOT). The positive response to the TAOT, with the reversal of flow direction, are highly suggestive of major occlusive disease of the internal carotid artery. Barnes and others (1977) showed that, for angiographically proven lesions of greater than 50% of the internal carotid, the TAOT test was positive in 64% of patients. Gosling and King (1978) investigated the sensitivity of the TAOT examination in 200 patients with a broad distribution of atherosclerotic disease from minor irregularity to total occlusion of the internal carotid. The test was positive in only 15% of subjects.

Barnes and colleagues (1977) developed an improved periorbital examination which depends on the determination of flow direction in the frontal artery, manual compression of all external carotid branches, and common carotid compression. The technique is illustrated in figure 8. For diameter stenoses of greater than 50%, sensitivity was 98.7% with 64% for the simple TAOT examination. Barnes (1979) discussed these results in detail and showed that, for both minor and major stenoses, the Doppler examination is only 56% sensitive in detecting carotid disease of potential clinical significance. He further showed the predictive value of this type of examination in the selection or exclusion of patients for carotid endarterectomy to be 39%. In other words, only 39% of those presenting with abnormal Doppler signals are candidates for carotid endarterectomy.

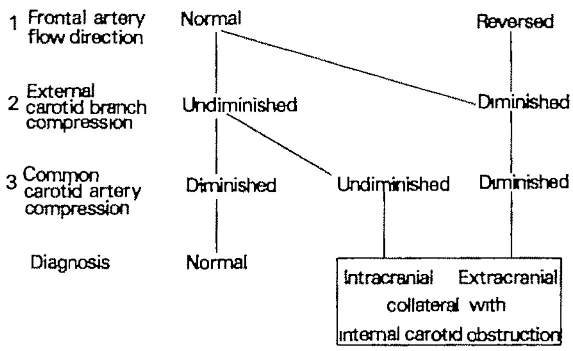
1 Frontal artery flow direction
Normal
Reversed
2 External carotid branch compression
Undiminished
Diminished
3 Common carotid artery compression
Diminished
Undiminished
Diminished
Diagnosis
Normal
Intracranial Extracranial collateral with internal carotid obstruction

FIG. 8. Improved periorbital examination procedure (Barnes et al., 1977).

Duplex scanning

The Duplex system was described in detail earlier. It consists basically of a real-time B-scanner with an incorporated pulsed Doppler flowmeter. An example of the imaging capability of this type of system is shown in figure 9. Figure 10 illustrates how the addition of the Doppler flowmeter helps in the diagnosis. There is no flow signal from the internal carotid artery.

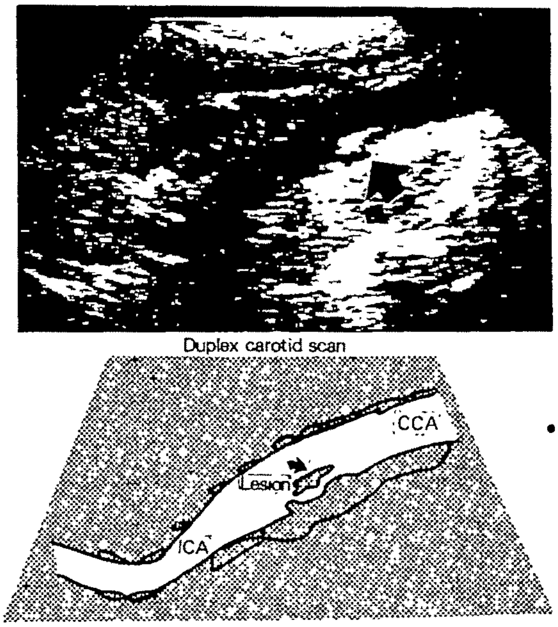

FIG. 9. Real-time B-scan image of a plaque at the origin of the internal carotid artery (ICA). CCA = common carotid artery.

Blackshear and colleagues (1979) compared Duplex scanners with contrast arteriography, in the assessment of the degree of stenosis of the carotid arteries. Overall sensitivity of the Duplex system was assessed as 84%.

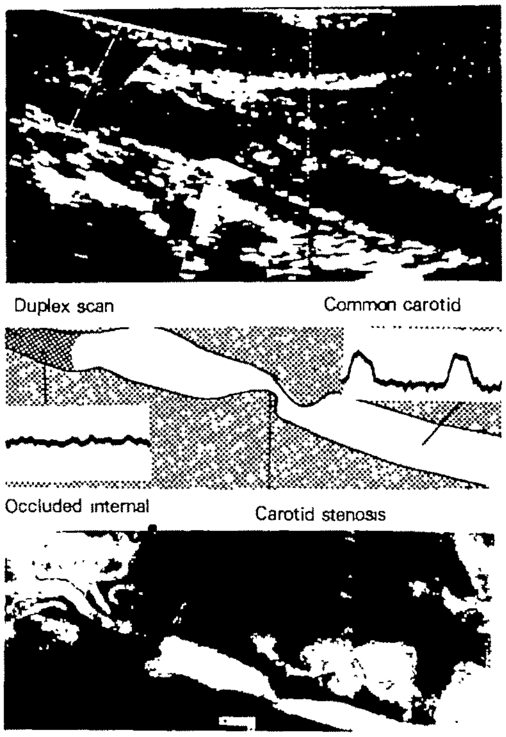

FIG. 10. Real-time B-scan of a major stenosis of the common carotid artery showing blood-velocity/time waveforms recorded from the common, but zero flow from the internal carotid.

Lusby and others (1981) investigated a series of 46 patients with a history of transient ischaemic attacks, and compared the results of Duplex scanning against carotid angiography. The results are shown in table I. The overall sensitivity and specificity was approximately 90%.

TABLE I. *Accuracy of real-time scanning compared with angiography*

Angiographic findings	No. of vessels	Agreement No.	Agreement %	False positive
Normal	10	9	90	1
0–25%	14	12	85	—
26–50%	10	9	90	—
51–99%	10	8	80	—

Doppler scanners

It was shown that Doppler imaging systems produce a functional image of moving blood inside a blood vessel. It is important to realize at this stage that no surrounding anatomy is displayed. Doppler scanners can operate either in a continuous wave mode (Reid and Spencer, 1972) or in a pulsed mode (Mozerskey et al., 1971). It has already been shown that continuous wave systems can produce projections of the blood vessel in only one plane, whereas the pulsed systems can visualize in three dimensions.

Two examples of images produced by a multichannel system are shown in figure 11A and B, with the contrast arteriogram for comparison. The Doppler images were produced independently of the arteriograms. Figure 11A shows an anterior–posterior view of the carotid bifurcation with a large plaque at the origin of the internal carotid. Figure 11B shows an area of calcification in the A–P view and a minor stenosis at the origin of the internal carotid, as shown in the lateral view. Blackshear and colleagues (1979) and Lusby and colleagues (1981) compared pulsed Doppler imaging systems with contrast arteriography. The former found a sensitivity of 75%, the latter of 88%, in detecting all grades of disease.

Spencer and colleagues (1977), Shoumaker and Block (1978) and White and Curry (1978) all compared continuous wave Doppler scanners with contrast arteriography. Woodcock (1981) has summarized their results and shows that, for diameter stenoses of less than 50%, pulsed systems are more sensitive than continuous wave. This is probably a result of the three-dimensional imaging capability of the pulsed type. It is sometimes difficult to image small stenoses in the anterior–posterior plane, but they are usually detected in the lateral display, as illustrated in figure 12. This is one of the major reasons for choosing the pulsed Doppler imaging system over the continuous wave. Figures 13 and 14 show a direct comparison between the contrast arteriogram, the Doppler image and the Duplex scan. All three imaging modalities were obtained by separate independent investigations.

Summary and conclusions

Evidence has been produced in the preceding sections to show that there is clinically useful diagnostic information contained in the Doppler-shift signal itself. Its variation over the cardiac cycle can be quantitated either as some parameter obtained from the maximum frequency envelope, such as the A/B ratio, or as the degree of spectral broadening. Periorbital investigations show that for stenoses of greater than 50% of the lumen the

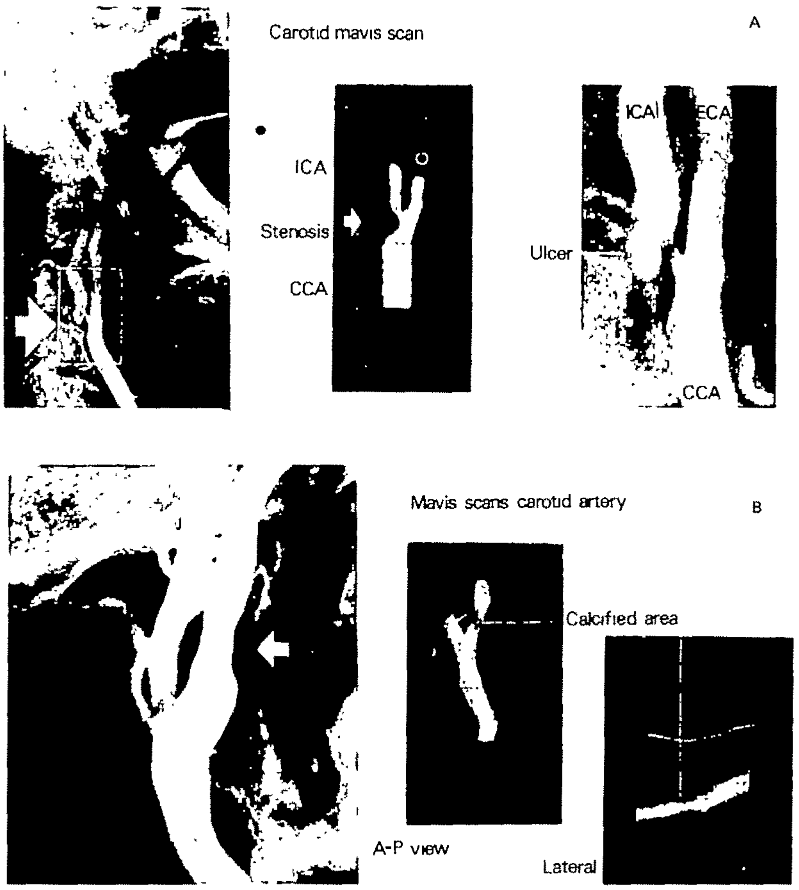

FIG. 11. A: Anterior–posterior view showing a large plaque at the origin of the internal carotid (ICA); B: anterior–posterior and lateral views showing calcification and minor stenosis at the origin of the internal carotid artery. ECA = external carotid artery.

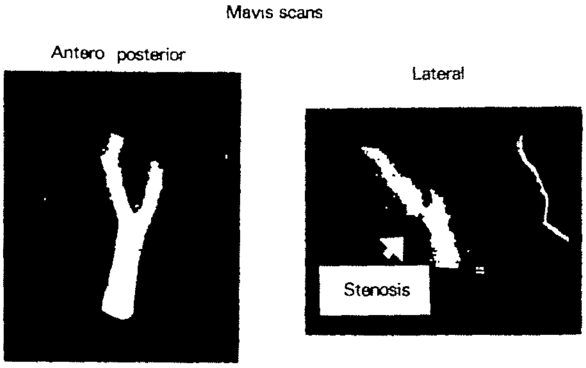

FIG. 12. Small stenoses can often not be visualized in the A–P view, but can usually be detected in the lateral scan.

improved compression test detects approximately 99% of angiographically demonstrable disease. Both the Duplex systems and the pulsed Doppler imaging systems have sensitivities around 90% for the detection of arterial disease around the carotid bifurcation. These results are summarized in table II. It can be seen that spectral broadening is the most sensitive technique for the detection of minor stenosis. If such a technique is used in conjunction with either the Duplex or the pulsed Doppler imaging system, the sensitivity of the combined techniques to small degrees of stenosis should be improved.

Investigation of arteries in the lower limb

In the investigation of occlusive arterial disease in the lower limb, the two types of imaging system and the blood-velocity/time waveform information over the cardiac cycle supply valuable diagnostic information.

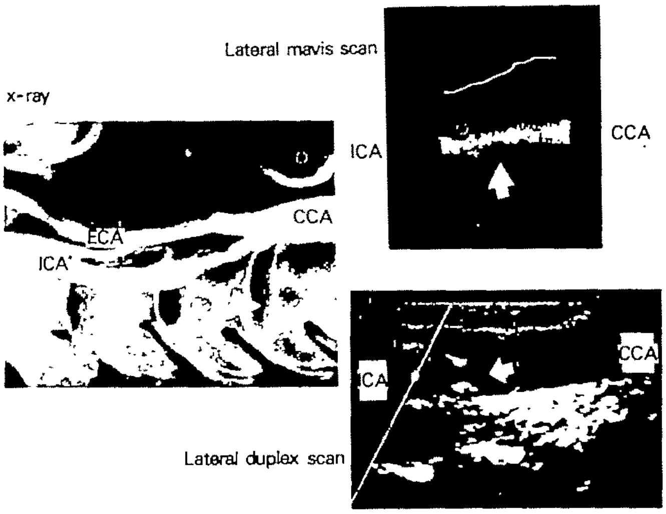

FIG. 13. Comparison of angiogram, Doppler image and the real-time scan.

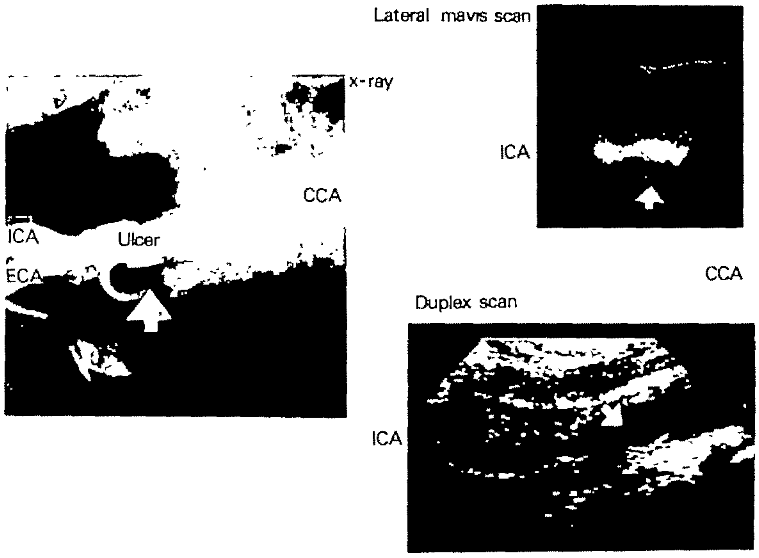

FIG. 14. Doppler image, real-time B-scan and angiogram, for comparison.

Blood-velocity/time waveform over the cardiac cycle

Strandness and others (1967) described qualitatively the changes in shape of the blood-velocity/time waveform over the cardiac cycle, proximal to, distal to, and over an occlusion of the profunda femoral artery. Since then various attempts have been made to quantify waveform shape in occlusive disease of the lower limb. Woodcock, Gosling and FitzGerald (1972) have shown how, by measuring the time delay between flow occurring at two points along the limb, combined with the calculation of the Pulsatility Index (PI) of the waveforms at each site and the Damping Factor (Δ), it is possible to differentiate between an occluded artery, generalized narrowing, and localized plaques. Pulsatility Index was originally defined in terms of Fourier analysis, but Gosling and King (1975) have simplified the calculation and redefined PI as being the peak-to-peak excursion of the waveform divided by the mean height (fig. 15). Damping Factor is defined as the PI at the proximal measuring site divided by the PI at the distal site.

TABLE II. *Comparison of all non-invasive tests in the detection of carotid artery stenosis. These, where possible, are the pooled results from various clinical and research groups*

Investigation	Percentage correct diagnosis at different degrees of stenosis		
	<50	>50	Occlusion
Abnormal flow direction	—	—	85
Temporal artery occlusion test	9	64	64
Improved occlusion test	—	98	98
CW Doppler imaging	23	84	87
Pulsed Doppler imaging	65	80	92
Duplex scanning	74	95	92
Spectral broadening	80	96	—

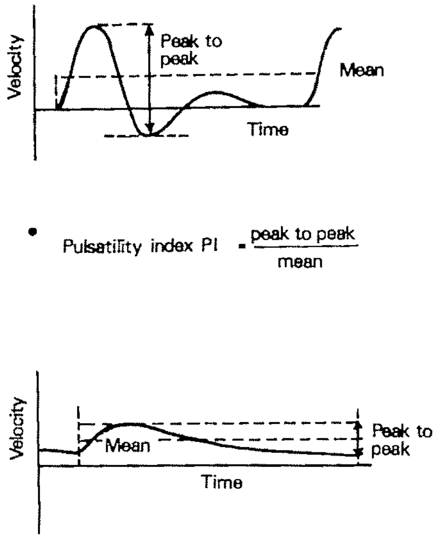

FIG. 15. Calculation of Pulsatility Index.

Gosling and King can now claim correct differential diagnosis in 89% of diseased lower limbs, using this modified technique.

Skidmore and Woodcock (1980a) have described a mathematical model, derived from Doppler signals in the lower limb, which defines the waveform shape in terms which are related to arterial elasticity, vessel lumen and peripheral impedance. This technique describes the physiological changes taking place to produce a given change in waveform shape (see also Skidmore and Woodcock, 1980b). The blood-velocity/time waveform recorded from the common femoral artery is digitized and the finite, discrete Fourier transform calculated. The equivalent Laplace transform is then evaluated by means of a curve-fitting procedure, and is found to be of the form:

$$\frac{1}{(S^2+2\delta\omega_0 S+\omega_0{}^2)(S+\gamma)}$$

The curve fitting is carried out on a small digital computer which calculates the values of the coefficients of the equation which gives the best fit to the original frequency distribution. This relationship is usually expressed graphically by plotting the positions of the poles on the Argand diagram, as shown in figure 16. It has been shown that ω_0 is related to the elastic properties of the major conduit arteries, γ to the distal impedance and δ to the radius of the ilio-femoral arterial segment (Skidmore and Woodcock, 1980a, b). The term δ is called the Laplace Transform Damping (LTD). This LTD term is very sensitive to the presence of occlusive arterial disease.

Baird and colleagues (1980) have compared the sensitivity and specificity of Pulsatility Index and Laplace Transform Damping using receiver operator characteristic curves (ROC). An estimate of the true-positive and false-positive rate in detecting stenotic lesions of greater than 50% was obtained using stepwise threshold criteria of PI and LTD. The sensitivity and specificity of the two ultrasound tests were thus compared whilst avoiding reference to a single arbitrary value. LTD values correlated well with the severity of iliac artery stenosis ($r = -0.75$). There was a significant difference between minor stenoses (<50% diameter, LTD = 0.5 ± SD 0.15) and major stenoses (>50%, LTD = 0.78 ± SD 0.16) ($P < 0.02$). There was a highly significant difference between the normal volunteers and patients with minor iliac disease ($P < 0.001$). LTD was not affected by an increased distal impedance and there was good correlation ($r = -0.73$) with iliac stenosis in the presence of an occlusion of the superficial femoral artery. Mean PI values for both minor (7.4 ± SD 4.2) and major (3.6 ± SD 1.6) stenoses were within the normal range. There was a good correlation with iliac stenosis if the distal vessels were patent ($r = 0.75$), but if the SFA was occluded, PI did not correlate with the presence or extent of iliac disease ($r = 0.51$).

The ROC curves are shown in figure 17. The LTD curve is better than PI, since it passes closer to maximum sensitivity and specificity. At an LTD value of 0.6, sensitivity was 85% and specificity

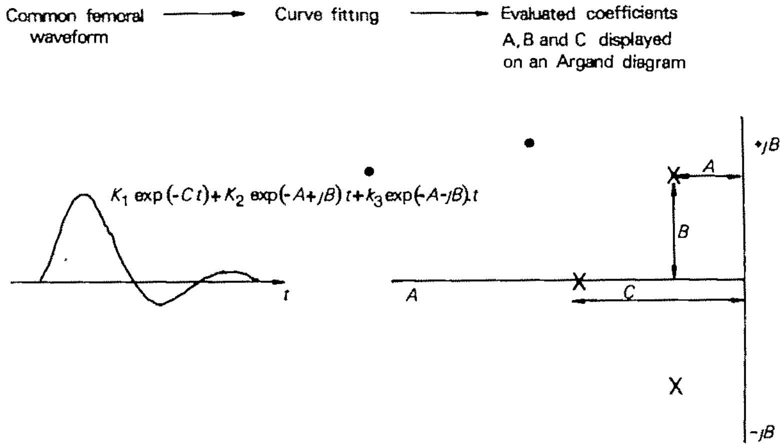
Common femoral waveform
Curve fitting
Evaluated coefficients A, B and C displayed on an Argand diagram
$K_1 \exp(-Ct) + K_2 \exp(-A+jB)t + K_3 \exp(-A-jB)t$
t
A
A
B
C
X
+jB
-jB

FIG. 16. Characterization of the blood-velocity/time waveform and the subsequent pole positions on the Argand diagram.

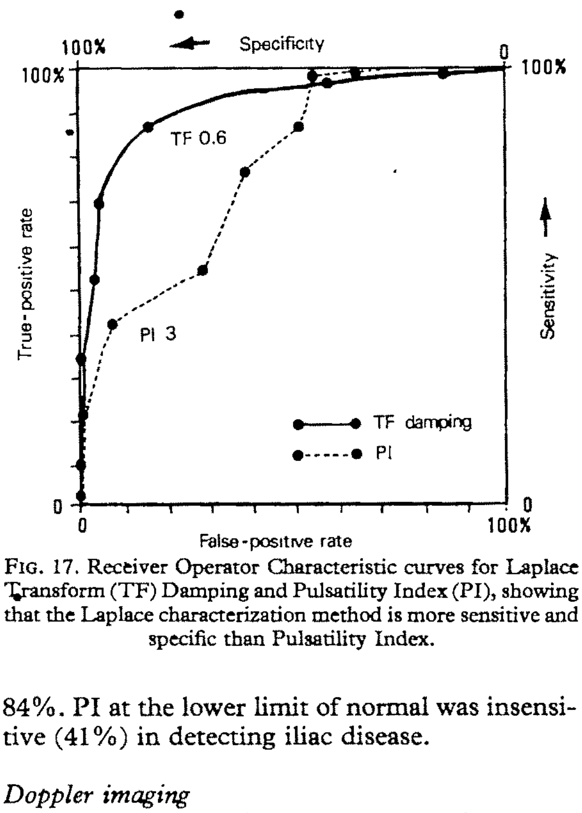

FIG. 17. Receiver Operator Characteristic curves for Laplace Transform (TF) Damping and Pulsatility Index (PI), showing that the Laplace characterization method is more sensitive and specific than Pulsatility Index.

84%. PI at the lower limit of normal was insensitive (41%) in detecting iliac disease.

Doppler imaging

Mozerskey and others (1971, 1972) have produced Doppler images of the iliac, common, superficial and profunda femoral arteries, and saphenous vein by-pass grafts. Fish (1972) produced cross-sectional Doppler images of the popliteal artery. Baird and colleagues (1979), using a pulsed Doppler imaging system, produced images of the femoral artery bifurcation and arterial grafts of the lower limb. In the investigations of the femoral artery bifurcation, lateral, cross-sectional and antero-posterior scans were obtained of the common femoral, superficial femoral and profunda femoral arteries, and blood-velocity/time waveforms were recorded from the centre stream in each artery. Pulsatility Index and Damping Factor, were then calculated. In 12 limbs in which the profunda femoral origin was later seen to be normal at operation, the common femoral to profunda femoral damping factor was invariably less than 1.4 (mean 0.96 ± SD 0.05). In 13 limbs of normal patients without clinical evidence of atherosclerosis, the damping factor was less than 1.34 (mean 0.92 ± SD 0.05). In eight limbs, at operation the profunda femoral was found to be completely occluded or severely stenosed (>50%). In these limbs the damping factor was always greater than 1.5 (mean 1.74 ± SD 0.08). Single plane arteriography of seven limbs correctly identified all three complete occlusions, but only one of four severe stenosis.

The internal diameter of 21 arterial grafts, 14 aorto-iliofemoral and seven axillobifemoral, was compared with 14 iliopopliteal grafts. All grafts, at implantation, were 10 mm i.d. The iliopopliteal grafts were reduced to 7.6 ± SD 0.4 mm at the inguinal level and to 6.3 ± SD 0.4 mm just above the popliteal anastomosis. No distal narrowing was found in any of the 14 aortofemoral grafts. Twenty-five internal diameter measurements of 14 iliopopliteal grafts were made up to 5 years after implantation. Sequential measurements in time were made on several grafts and popliteal narrowing was found to be progressive with time ($r = -0.54$; $P < 0.01$). The inguinal internal diameter of the axillobifemoral grafts was not reduced.

These figures support the known patency rates of aortofemoral and iliopopliteal grafts. The long-term patency rates of aortofemoral grafts are 74% at 5 years and 66% at 10 years, whereas the 2-year patency rate of iliopopliteal grafts is 60% (Bird, Skidmore and Woodcock, 1979).

A Doppler scan of the femoral bifurcation is shown in figure 18. Figure 19 shows the Doppler scan of the common femoral and profunda femoral artery, together with the corresponding arteriogram and the maximum blood-velocity/time waveforms recorded from these vessels.

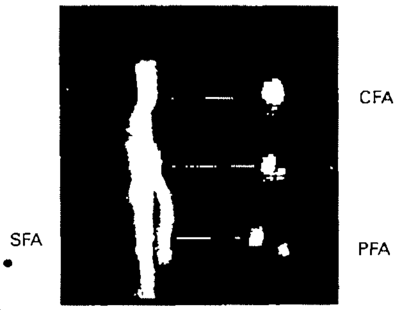

FIG. 18. Anterior–posterior and cross-sectional images of the femoral bifurcation. CFA = common femoral artery; PFA = profunda femoral artery; SFA = superficial femoral artery.

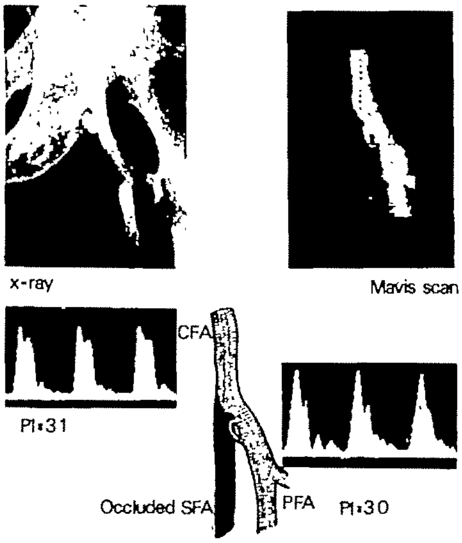

FIG. 19. Doppler image of the profunda femoral artery in comparison with the femoral angiogram. The maximum blood-velocity/time waveforms recorded from the common and profunda femoral arteries are also shown.

Duplex scanning

At present no comparisons have been carried out between Doppler imaging, Duplex imaging and contrast arteriography, in the lower limb. However, it is extremely unlikely that these comparisons would differ considerably from similar studies reported previously in the carotid artery. A direct comparison of the two ultrasonic systems in imaging a Dacron graft in the lower limb is shown in figure 20. Both images show a wide-bore, patent graft. Clifford and colleagues (1981) have reported investigations carried out on grafts in the lower limb using both imaging systems and have shown that it may be possible to estimate the growth of neo-intimal hyperplasia.

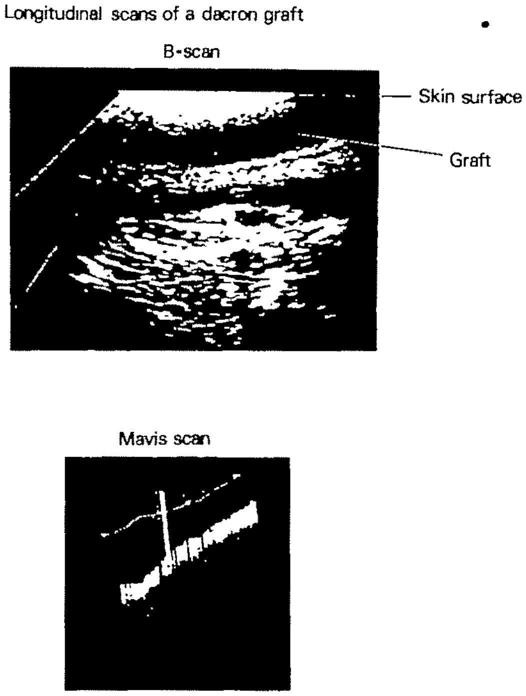

FIG. 20. Direct comparison of Doppler and real-time images of a Dacron graft.

Conclusions

The assessment of the severity of arterial disease in the lower limb can best be achieved by combining the information obtainable from the shape of the blood-velocity/time waveform over the cardiac cycle with an image of the blood vessel using either the Duplex or the Doppler imaging system. Using a combination of all three techniques, it should be possible to study the rate of growth of neo-intimal hyperplasia in arterial grafts. Up until the present time it has not been possible to study this non-invasively.

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PREOPERATIVE ASSESSMENT OF THE PATIENT WITH CARDIOVASCULAR DISEASE

P. Foëx

The morbidity and mortality of anaesthesia and surgery are increased by cardiac diseases. It is essential, therefore, to recognize the presence of cardiovascular diseases and to assess their severity in order to prevent serious complication during anaesthesia and the period after operation. Relatively silent cardiac or vascular diseases are often first diagnosed during the preoperative visit (Kyei-Mensah and Thornton, 1974; Frost, 1976). Where the diagnosis has already been made it is important to evaluate the severity of heart disease, to determine whether or not medical treatment could further improve cardiac function (Howat, 1971; Friedlander, 1973) and to consider the pathophysiology of the disease. The optimal anaesthetic management and the decision on invasive monitoring rest on the correct diagnosis of the disease and of its repercussions on the circulation. Detailed medical history and careful clinical examination, supplemented by electrocardiogram and chest x-ray, form the basis of evaluation before operation and may have to be complemented by echocardiography, cardiac catheterization and angiography.

ISCHAEMIC HEART DISEASE

Coronary heart disease causes more than 160 000 deaths each year in the United Kingdom. The frequency of coronary artery disease is very high and the disease may not be clinically apparent unless several vessels are obstructed. Cardiac function may be impaired in almost asymptomatic patients. Presence of coronary heart disease causes a two- to three-fold increase of perioperative mortality and a 10-fold increase in coronary occlusion after surgery. The risk of postoperative infarction is particularly high when surgery takes place within a few months of a previous infarction. Improvements in anaesthetic management have reduced the frequency of reinfarction from almost 100% in 1962 (Knapp, Topkins and Artusio, 1962) to 6% (Steen, Tinker and Tarhan, 1978). However when surgery takes place within the first 2 months of infarction, reinfarction is common and its mortality is about 60%. Reinfarction is more frequent after thoracic or abdominal surgery, prolonged operation and after episodes of intraoperative hypo- and hypertension (Steen, Tinker and Tarhan, 1978). These factors had already been identified in 1964 by Chamberlain and Edmonds-Seal in their study of electrocardiographic abnormalities after operation. The long-term prognosis of infarction is worse in patients who have developed arterial hypertension, atrial or ventricular arrhythmias or transient renal failure (Luria et al., 1976); their operative risk also is likely to be increased.

Coronary heart disease must be suspected even in the absence of symptoms when predisposing factors are noted. The risk of developing major coronary events is increased two-fold by smoking, four-fold by the combination of smoking and hypertension, and eight-fold when smoking, hypertension and hyperlipidaemia are all present (Stamler and Epstein, 1972). Diabetes, occlusive vascular events and family history of ischaemic heart disease are other important predisposing factors.

The diagnosis of coronary heart disease rests on a history of angina pectoris or electrocardiographic evidence of myocardial ischaemia or infarction. Angina, described as a retrosternal, painful sensation of pressure, constriction or tightness, irradiating towards left arm, lower jaw or throat, is easily recognized. The frequency and duration of attacks should be noted. An increased frequency or duration of angina or a reduced exercise tolerance indicate the development of unstable angina and the operative risks may be similar to those of patients with recent infarction.

Between anginal attacks, clinical examination may reveal a fourth heart sound, an enlarged left ventricle and a weak apex contraction reflecting reduced wall motion. Signs of left ventricular failure may be observed.

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The electrocardiogram can be completely normal between attacks of angina unless the patient has suffered previous myocardial infarction. However, in 80% of patients it is abnormal. Nonspecific abnormalities such as signs of left ventricular hypertrophy, bundle branch blocks and atrio–ventricular conduction disorders must be taken seriously; they may be caused by coronary artery disease. Specific abnormalities include pathological Q waves, abnormal ST segments and J point (fig. 1) (Chaitman et al., 1979) and ischaemic alterations of T waves, and confirm the diagnosis. The unexpected regression of R waves in the precordial leads may indicate the presence of non-transmural infarction and is not always recognized. Acute ischaemic alterations of the electrocardiogram suggesting myocardial infarction can be observed in the absence of symptoms: silent infarction is far from exceptional in patients with vascular disease and increases the operative risks to unacceptable levels. Comparison of sequential e.c.g. tracings is important to detect recent myocardial ischaemia and also to identify persistent ST segment elevations associated with ventricular aneurysms. Further evaluation of cardiac function, for example by echocardiography, is necessary when ventricular aneurysm is suspected. Arrhythmias must be recognized. In the context of ischaemic heart disease, ventricular premature beats are associated with sudden death (Kotler et al., 1973), left venticular dysfunction (Sharma, Ballantyne and Goldstein, 1974) and reduced ejection fraction (Schultze et al., 1975), their treatment should be considered before surgery.

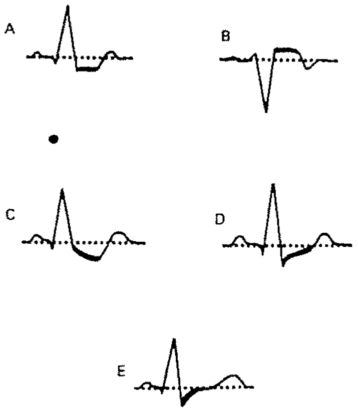

FIG. 1. Abnormalities of ST segments may be observed in coronary heart disease. Horizontal depression of ST segment (A), horizontal elevation of ST segment (B), descending ST segment (C), and slowly ascending ST segment (D), are characteristic of myocardial ischaemia, while rapidly ascending ST segment (E) may occur during exercise in the absence of coronary artery lesions.

When either the medical history is suggestive of coronary heart disease or predisposing factors are recorded but the electrocardiogram is normal, it is often suggested that confirmation of the diagnosis may be obtained using an exercise e.c.g. The test is considered positive if ST segment depression greater than 0.1 mV develops. The test is considered both specific and sensitive, but carries a risk and must be discontinued if angina develops. However, when compared with coronary angiography, the exercise test may give false positive as well as false negative results (Borer et al., 1975). Because of these limitations, it is often possible to evaluate the severity of ischaemic heart disease only in terms of frequency of attacks of angina, of limitation of physical activity and a history or evidence of myocardial infarction. It must be stressed that the persistence of angina after myocardial infarction increases postoperative morbidity and mortality respectively two- and fourfold by comparison with those of patients with well compensated infarction (Ponka, 1977).

Abnormalities of wall motion (hypokinesia, akinesia and dyskinesia) are frequently observed in patients with coronary heart disease and can be detected by ventriculography (fig. 2) and by non-invasive techniques (Swan, 1979). In up to 60% of patients minor abnormalities of wall motion can be detected at rest, while in up to 86% of patients more pronounced ventricular wall dysfunction occurs during exercise (Lindsay et al., 1980) and the ejection fraction is markedly reduced. The non-invasive techniques rely on radionuclides (radionuclide cineangiography), ultrasonics (bidimensional echocardiography) and magnetic inductance (cardiokymography), and are of proven value (Borer et al., 1977; Righetti et al., 1980; Silverberg et al., 1980). With these techniques systematic studies of wall function will become easier and will contribute greatly to the assessment of patients with coronary disease. This may become even more relevant if experimental studies showing that anaesthetic agents can cause dysfunction of myocardium supplied by a narrowed coronary artery (Lowenstein et al., 1979; Cutfield et al., 1980; Francis et al., 1980) are confirmed in man.

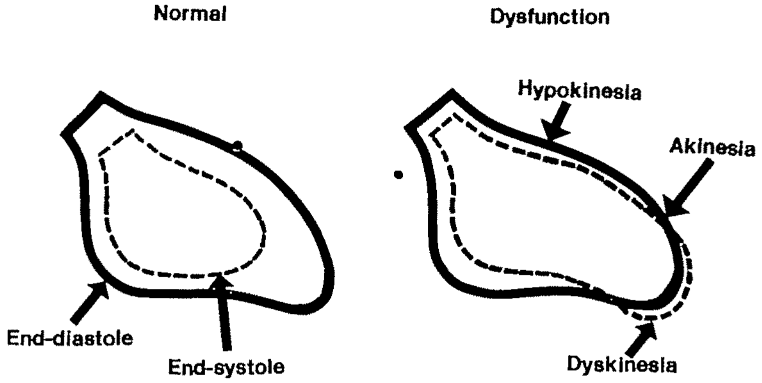

FIG. 2. Angiographic studies have shown that the normal pattern of left ventricular wall function represented by the outline of left ventricular cavity at end-diastole and end-systole (left panel) may be profoundly altered in the case of coronary artery disease. In some areas, wall function is reduced (hypokinesia), abolished (akinesia) or, paradoxical (dyskinesia), as shown on the right panel.

Assessment before operation must include a review of the patient's medication. The problems associated with digitalis and adrenergic beta-receptor antagonists will be discussed separately. Calcium antagonists have been introduced relatively recently in the treatment of coronary heart disease, particularly where coronary artery spasm appears to play an important role. They are inhibitors of inward calcium currents of smooth muscle and cardiac muscle cells. They cause peripheral and, most importantly, coronary vasodilatation, but they limit the amount of calcium made available for interaction with the contractile proteins and, therefore, reduce myocardial contractility and myocardial oxygen demand. There are few data on the interactions between calcium antagonists and anaesthesia (Patschke et al., 1977), but the reduction of vascular resistance accompanied by myocardial depression may cause hypotension.

Anaemia is another risk factor. It causes a hyperdynamic state of the circulation accompanied by a large increase in myocardial oxygen consumption. Oxygen supply to the myocardium is adequate only as long as coronary blood flow is increased. In the case of narrowed coronary vessels, anaemia may cause wall dysfunction (Hagl et al., 1977) and its presence increases the risk of complications.

In ischaemic heart disease, autoregulation of the coronary circulation is impaired by the narrowing of the coronary vessels. The major contributing factors to imbalance of oxygen supply and oxygen demand and thus to myocardial ischaemia, are:

(1) hypotension (reduction of flow through narrowed vessels can be greater than the reduction of oxygen demand);
(2) hypertension (increased demand cannot be met by similar increases of flow);
(3) tachycardia (demand is increased and supply is reduced because of the shorter duration of diastole);
(4) left ventricular overload (increased oxygen demand as a result of higher venticular diastolic pressure, while oxygen supply is decreased because of the reduction of the coronary perfusion pressure, the difference between aortic diastolic and ventricular diastolic pressure).

HYPERTENSIVE HEART DISEASE

Systemic arterial pressure in the adult represents a continuum without sharp dividing lines between normo- and hypertension. However, it is generally agreed that values of arterial pressure greater than 150 mm Hg systolic and 90 mm Hg diastolic on three successive occasions establish the diagnosis of arterial hypertension. The frequency of arterial hypertension varies between 13% and 41% of the population (National Health Survey, 1964; Tibblin, 1972) and the frequency of cardiovascular complications is proportional to the level of hypertension (Anderson, 1978). Severe arterial hypertension (greater than 180/100 mm Hg) is observed in as many as 11% of surgical patients (Kyei-Mensah and Somanathan, 1976).

Straightforward determination of cuff arterial pressure is easy, yet approximately 50% of hypertensive patients are not diagnosed, 50% of those diagnosed are untreated and 50% of those treated are inadequately controlled. Thus, arterial hypertension remains one of the commonest causes of cardiovascular deaths. Approximately 60% of hypertensive patients die from acute myocardial infarction, 30–40% of a cerebrovascular accident and about 10% from other causes (Hollander, 1973; Bulpitt et al., 1979).

The symptoms and signs of arterial hypertension relate to involvement of the main target organs: heart, brain and kidneys, and depend upon the primary or secondary nature of the disease.

The cardiac complications of arterial hypertension are coronary artery disease and left ventricular hypertrophy. Clinical examination may reveal an enlarged heart and signs of left ventricular failure. The chest x-ray may confirm left ventricular hypertrophy and may reveal aortic calcifications often associated with coronary artery lesions. The electrocardiogram will confirm the presence of left ventricular hypertrophy with or without strain. Disorders of intraventricular conduction, signs of myocardial ischaemia and of myocardial infarction are frequently observed.

The cerebral complications of arterial hypertension include transient ischaemic attacks and major cerebrovascular accidents; they will be discussed separately.

Impairment of renal function is more difficult to assess clinically. A history of nocturia may indicate chronic renal involvement, but there may be no sign of advanced renal disease until uraemia develops. Blood urea and creatinine concentrations are significantly increased only when 70% of total renal function has been lost. Serum electrolytes, urea and creatinine should be measured together with creatinine clearance. Careful urinalysis is also necessary, with close attention to proteinuria, abnormal urinary sediment and inability to concentrate urine.

The retina is another target organ. Diminution of the calibre of small vessels, segmental constriction of the arterioles and arteriovenous nipping are all observed in hypertensive patients. Flame-shaped haemorrhages and glistening white exudates indicate a more advanced stage, while papilloedema may herald the final stage of the disease.

About 90% of hypertensive patients suffer from primary or essential hypertension and only fewer than 10% of secondary hypertension. However, enquiry should be directed to determine the nature of arterial hypertension, since the latter will influence the anaesthetic management of the patient. Renal causes fall into three categories: renal parenchymal diseases, renovascular disease, and other severe renal diseases. A full evaluation of renal function must be obtained. It must be remembered that renal function will be further impaired during the period after operation and that fluid and electrolyte balance will be particularly difficult to maintain. An important hazard in these patients is the development of hyperkalaemia.

Endocrine causes of hypertension form another important group. The excessive release of catecholamines by the adrenal medulla, in cases of phaeochromocytoma, may be paroxysmal or stable. Patients suffering from phaeochromocytoma, may present with typical paroxysms of hypertension, accompanied by tachycardia, palpitations, malaise, apprehension and sweating. In other patients the increase of arterial pressure is stable and associated with heat intolerance and signs of hypermetabolism. Confirmation is obtained from studies of plasma catecholamines and determinations of excretion of vanillylmandelic acid (VMA), catecholamines and metanephrine. If the presence of a phaeochromocytoma is not recognized and the patient is not prepared adequately, anaesthetic and surgical manoeuvres are likely to cause life-threatening complications such as myocardial infarction, intracerebral haemorrhage and cardiac failure.

Arterial hypertension may result from over production of gluco- and mineralocorticoids by the adrenal cortex. The clinical features of Cushing's disease are easily recognized and it is important to be aware of the possibility of diabetes, hypokalaemia and osteoporosis, because these are common complications. Low potassium stores combined with muscle wasting caused by increased protein catabolism result in muscle weakness. This may severely interfere with adequate pulmonary ventilation in the period after operation. In primary hyperaldosteronism (Conn's syndrome), the excessive production of aldosterone promotes sodium retention and causes losses of potassium and hydrogen ions. The hypokalaemic alkalosis facilitates the development of arrhythmias and the low potassium stores are responsible for muscle weakness. In both Cushings syndrome and Conn's syndrome, repletion of the potassium stores is essential before surgery.

Amongst other causes of arterial hypertension, aortic coarctation must also be considered. Blood flow to the territories distal to the obstruction, particularly to the kidneys, is maintained because of arterial hypertension and because of collateral channels connecting vessels above and below the obstruction. The diagnosis is often made on routine physical examination revealing arterial hypertension, forceful carotid pulsation, delayed or absent femoral pulses, collateral vessels around the scapula and signs of left ventricular enlargement. Patients with aortic coarctation are at risk of developing congestive heart failure, bacterial endocarditis, hypertensive encephalopathy and cerebrovascular accidents. Hypertensive responses to anaesthetic or surgical manoeuvres could precipitate life-threatening complications.

Treatment of arterial hypertension has improved the life expectancy and reduced the frequency of cerebrovascular and renal complications. Withdrawal of antihypertensive therapy may cause severe exacerbations of the hypertensive disease (Katz, Croneau and Barash, 1976; Bruce, Croley and Lee, 1979), while maintenance of treatment up to and including the day of anaesthesia and surgery makes the cardiovascular state of the hypertensive patients more stable (Prys-Roberts, Meloche and Foëx, 1971). This attitude is now accepted and it is very important to understand the pharmacology of antihypertensive agents. Thiazides are widely used in the treatment of hypertension and may induce hypokalaemia, hyperuricaemia and hyperglycaemia. Noradrenaline-depleting drugs (guanidine anlogues and rauwolfia alkaloids) decrease the effects on the circulation of indirect-acting pressor amines such as ephedrine, while they exaggerate the effects of direct-acting pressor amines (noradrenaline, methoxamine, metaraminol, phenylephrine). Vasodilators tend to cause tachycardia. Adrenergic beta-receptors are widely used in the treatment of hypertension and will be discussed later. Clonidine causes central sympathetic inhibition; sudden withdrawal may cause severe rebound hypertension (Hansson and Huynor, 1973) and thus it is essential to continue the normal dosage throughout the period of operation, if necessary by i.v. or i.m. administration (Bruce, Croley and Lee, 1979; Kaukinen, Kaukinen and Eerola, 1979).

The ideal situation is that of treated, well controlled hypertension. What should be the attitude for untreated hypertensive patients? In those with moderate hypertension (diastolic arterial pressure between 90 and 100 mm Hg), and in the absence of clinical signs of cardiac, renal or cerebrovascular involvement, there is no evidence that treatment of arterial hypertension reduces the frequency of complications after surgery (Goldman and Caldera, 1979). In those with severe hypertension, elective surgery should be postponed and hypertension brought under control. In emergencies haemodynamic responses to anaesthesia can be minimized by the careful use of anaesthetic agents and of cardiovascular drugs, (including, where necessary, vasodilators and adrenergic beta-receptor antagonists) with monitoring of e.c.g., arterial pressure and, in some cases, the pulmonary wedge pressure (Prys-Roberts and Meloche, 1980).

VASCULAR DISEASE

Patients with peripheral vascular disease suffer from a generalized disease and the life-threatening complications include myocardial infarction and cerebrovascular accidents.

Cerebrovascular disease

Looking for signs of previous cerebrovascular accidents is imperative, but not sufficient to assess patients with cerebrovascular disease. The patients should be questioned carefully regarding any history of transient disturbances of neurological function.

Transient ischaemic attacks have a brief duration, tend to resolve spontaneously without residue and usually recur. When the initiating lesion is present in the distribution of the carotid arteries, a history of brief contralateral hemiparesis or monoparesis may be elicited, at times accompanied by monocular blindness on the side of the lesion. When the stenotic lesion is in the vertebrobasilar distribution, the most common manifestations are vertigo, often accompanied by dimming or loss of vision and "drop attacks". Particular attention should be paid to reduced carotid artery pulsation and to carotid artery bruits. These signs could indicate the presence of carotid artery stenosis. Cerebral infarction could follow the development of hypotension during operation (Tufo, Ostfeld and Shekelle, 1970; Carney et al., 1977). Like postoperative myocardial infarction, the prognosis of postoperative stroke is very poor with about 50% mortality (Carney et al., 1977). The risk of stroke after operation is increased by previous cerebrovascular accidents (Corman, 1979).

Cerebrovascular disease as a result of surgically accessible lesions of the carotid arteries may be discovered in patients with severe coronary artery disease requiring coronary artery surgery. Prophylactic carotid endoarterectomy has been advocated as a preliminary to coronary artery surgery. Mortality of carotid artery surgery is very high in these patients (Braithwaite, 1975). When coronary artery and carotid artery surgery are performed during the same operation, the frequency of cardiac and cerebrovascular complications is low (Morris et al., 1978) and this must be borne in mind when cerebrovascular surgery is contemplated in patients with severe coronary heart disease.

Peripheral vascular disease

Occlusive vascular disease is most commonly caused by atherosclerosis or embolic occlusion. Thromboangiitis obliterans, collagen disease and other types of arteritis are much less frequent. In the case of aorto–iliac atheroma, the stenosis or occlusion is situated in the lower part of the abdominal aorta below the renal arteries. In case of femoro–popliteal atheroma, the lesions develop near the junction of the middle and distal thirds of the femoral artery and then extend proximally up the vessel as far as its femoris profunda branch. The clinical features of peripheral vascular disease of the lower extremities include intermittent claudication, diminution or absence of pulses, systolic bruits, ischaemic skin changes and muscle wasting. Claudication pain is classically felt in the calf (gastrocnemius and soleus), in the sole of the foot and, less frequently, in thighs and buttock. Claudication pain occurs after a definite amount of exercise. In the early stages of the disease hyperaemic responses are delayed but still adequate, and the patient is able to continue to walk. In more severe cases the patient must stop. Rest pain is a very ominous sign with regard to survival of the affected limb. All pulses should be felt and their intensity recorded. Oscillometry gives a crude indication of the amplitude of arterial pulsation, while examination with ultrasound gives a non-invasive quantitative estimation of blood flow. Auscultation for bruits should be performed over the entire length of the aorta. A bruit in the region of the umbilicus may indicate distal aortic or common iliac disease; in the mid-epigastrium and laterally it may reveal renal artery stenosis, and in the subxyphoid area it may relate to coeliac artery stenosis.

In the presence of severe peripheral vascular disease, the patient's activity can be so limited that even very severe coronary heart disease may remain asymptomatic. This should not be overlooked in the preoperative assessment.

VALVULAR HEART DISEASE

Only the basic pathophysiology of the most common valvular diseases will be described.

Aortic stenosis

Aortic stenosis causes a chronic pressure overload of the left ventricle characterized by concentric hypertrophy of the ventricular wall. The hypertrophic ventricle has reduced compliance. Myocardial oxygen demand is increased because of increased left ventricular mass, increased left ventricular pressure and prolonged ejection time, while coronary blood flow and oxygen supply are decreased by intramyocardial pressure (decreasing systolic coronary flow and impeding subendocardial blood flow) and by associated coronary artery disease. While tolerance to anaesthesia need not be reduced by mild or moderate asymptomatic aortic stenosis, it is greatly reduced by severe symptomatic aortic stenosis (Goldman et al., 1977). Depression of the myocardium by volatile anaesthetic agents and sudden reductions of peripheral vascular resistance may reduce coronary perfusion and cardiac output dramatically. Because of the relatively fixed stroke volume, bradycardia causes marked reductions of cardiac output; tachycardia compromises coronary flow by reducing the duration of diastole. Because of the reduced diastolic compliance, the atrial contribution to ventricular filling is an important determinant of cardiac output and arrhythmias such as junctional rhythms are poorly tolerated. Similarly, even modest changes in circulating volume have an adverse effect on cardiac performance.

Aortic stenosis associates a loud, rough, systolic murmur (second right interspace) with thrill, absent second aortic sound and slow-rising pulse. The apex thrust is forceful. Electrocardiographic signs of left ventricular hypertrophy and strain are present.

Aortic regurgitation

Aortic insufficiency imposes a chronic volume load to the left ventricle as the regurgitant flow from the aorta is added to normal ventricular filling from the left atrium. This increased load causes eccentric ventricular hypertrophy (wall thickness and size increase) and the ventricle becomes more compliant. The low aortic diastolic pressure may reduce coronary perfusion. Bradycardia accentuates regurgitation by increasing the duration of diastole, and is poorly tolerated. Resistance to left ventricular ejection being a major determinant of forward left ventricular flow, increases in peripheral vascular resistance decrease cardiac output and may precipitate cardiac failure.

Aortic insufficiency may be difficult to detect. The high-pitched diastolic murmur may be heard only when the patient leans forward. Wide pulse pressure and collapsing pulse are observed. The electrocardiogram reveals signs of left ventricular hypertrophy and strain.

Mitral stenosis

Resistance to blood flow through the narrowed mitral orifice causes chronic increase of left atrial pressure. The increased atrial pressure is reflected into the pulmonary circulation where pulmonary venous congestion and perivascular oedema develop, followed by hypertrophy and intimal sclerosis of the pulmonary vessels. Gradually, the signs of pulmonary venous congestion (haemoptysis, pulmonary oedema) are replaced by signs of systemic venous congestion (hepatomegaly, peripheral oedema). In severe mitral stenosis, stroke volume is relatively fixed and bradycardia can result in severe reductions of cardiac output. Tachycardia reduces the diastolic filling time and causes large increases in left atrial pressure, facilitating the development of pulmonary oedema. This risk is particularly important in case of fast atrial fibrillation. Administration of digitalis before operation has been advocated to minimize the risk of fast atrial fibrillation (Friedlander, 1973).

Physical signs of mitral stenosis include a loud, high-pitched first heart sound, exaggerated second pulmonic sound, short opening click and diastolic rumble with presystolic reinforcement. The electrocardiogram will confirm atrial hypertrophy (P mitrale) as long as sinus rhythm is present. Right axial deviation is usual.

Mitral regurgitation

During systole a large regurgitant flow occurs in the direction of the left atrium. The heart enlarges to accommodate the volume load and both atrial and ventricular compliance increase. With a very distended left atrium, large regurgitant flows are accommodated with little change of atrial pressure and the pulmonary vascular complications are minimized. However, in case of acute mitral regurgitation as a result of papillary muscle rupture or dysfunction or as a result of chordal rupture, pulmonary hypertension and right ventricular overload may develop very rapidly. Arterial hypertension increases the regurgitant flow and precipitates cardiac failure.

Physical signs of mitral regurgitation include faint apical first sound, blowing pansystolic murmurs extending into the axilla and strong apex beat. E.c.g. and chest x-ray confirm left atrial and left ventricular hypertrophy.

Patients with valve prosthesis

Replacement of diseased heart valves causes subjective improvement in 90% of the survivors. Radiological signs of cardiomegaly and of pulmonary hypertension, when previously observed, decrease gradually. In some patients slight stenosis of the replaced valve will develop; dysfunction because of thrombi or displacement may occur; thromboembolic accidents and mild haemolysis may develop. The frequency of embolic accidents is reduced by well controlled anticoagulation. During the first year after tricuspid or mitral valve replacement, anticoagulants should not be stopped unless haemostasis is likely to be very difficult or bleeding very dangerous. Changing from oral to parenteral anticoagulation with heparin has been recommended (Friedlander, 1973). The most serious risk in patients with valve prosthesis is that of endocarditis.

Prevention of endocarditis

The risk of endocarditis relates to host factors, characteristics of micro-organisms and degree of bacteraemia (Sipes, Thompson and Hooke, 1977). At highest risk are patients with left-sided valvular lesions, prosthetic valves, small ventricular septal defects, patent ductus arteriosus, tetralogy of Fallot and aortic coarctation. The presence of arteriovenous fistulae (haemodialysis shunts) and previous endocarditis increase the risk of infection. The frequency of bacteraemia is very high during prostatectomy, periodontal surgery, dental extraction, tonsillectomy, burns surgery and surgery of infected areas. Bronchoscopy with a rigid bronchoscope, nasotracheal intubation or endotracheal suction may cause bacteraemia in up to 15% of patients (Everett and Hirshmann, 1977). In patients at risk of developing endocarditis, all possible sites of infection must be investigated and eradicated before surgery. Antibiotic therapy should be based on all available data concerning the micro-organisms responsible for the focal infection. In the absence of infection, prophylactic antibiotic therapy is instituted. The recommendations of the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis of the American Heart Association (1977) are summarized in table I.

TABLE I. *Prophylaxis of bacterial endocarditis in adults*

Dental procedures and upper airway surgery
- Regimen A.
  - (1) *Combined oral-parenteral penicillin.* Aqueous crystalline penicillin G 1 mega unit i.m. mixed with procain penicillin G 600 000 units i.m., given 30–60 min before procedure. Penicillin V 500 mg 6-hourly for next 48 h.
  - (2) *Oral penicillin.* Penicillin V 2 g, 30–60 min before procedure. Follow with 500 mg 6-hourly for 48 h.
  - (3) *Patients allergic to penicillin.* Erythromycin 1 g, 1.5–2 h before procedure followed by 500 mg 6-hourly for 48 h, or Vancomycin (see below).
- Regimen B (recommended for patients with prosthetic valves)
  - (1) *Penicillin plus streptomycin.* Aqueous crystalline penicillin G 1 mega unit i.m. mixed with procain penicillin G 600 000 units i.m. plus streptomycin 1 g. i.m. given 30–60 min before procedure. Penicillin V 500 mg orally, 6-hourly for next 48 h.
  - (2) *Patients allergic to penicillin.* Vancomycin 1 g i.v. over 30–60 min started 30–60 min before procedure and followed by erythromycin 500 mg orally 6-hourly for 48 h.

Gastrointestinal and genito-urinary surgery and instrumentation
- (1) Aqueous crystalline penicillin G 2 mega units i.m. or i.v. or ampicillin 1 g i.m. or i.v. or gentamycin 1.5 mg kg^{-1} not exceeding 80 mg, i.m. or i.v. or streptomycin 1.0 g i.m.
- (2) *For patients allergic to penicillin.* Vancomycin 1 g i.v. given over 30–60 min plus streptomycin 1 g i.m., one dose 30 min before procedure. May be repeated in 12 h.

ARRHYTHMIAS AND CONDUCTION DISORDERS

Arrhythmias and heart block are often associated with organic heart disease.

Arrhythmias

Atrial arrhythmias are common and often considered relatively benign. However, atrial premature beats may precede the development of atrial tachycardia or atrial fibrillation; a wandering pace-maker may indicate the presence of organic heart disease or digitalis intoxication. Atrial fibrillation and flutter are usually associated with organic heart disease or with hyperthyroidism. Fast ventricular rates should always be brought back to normal values. The perioperative management of patients with atrial fibrillation is made difficult by the poor tolerance to fluid load. During major surgery monitoring of pulmonary wedge pressure is recommended (Sørensen and Engell, 1978).

Ventricular premature beats are often associated with organic heart disease or digitalis toxicity (particularly when they assume the pattern of bigeminy). Ventricular ectopic beats occurring during repolarization (R on T phenomenon) may start ventricular tachycardia or fibrillation and require immediate treatment. It must be stressed that atrial and ventricular arrhythmias contribute significantly to the cardiac risks of anaesthesia (Goldman et al., 1977).

Long QT interval

The upper limit for QT interval when corrected for heart rate is usually given as 0.44 s. Its prolongation may be associated with ventricular arrhythmias, syncope and sudden death. Prolongation of QT may be congenital (deafness, long QT, syncope, sudden death) or acquired. Prolongation of QT may be associated with electrolyte imbalance (hypokalaemia, hypomagnesaemia, hypocalcaemia) and with administration of drugs (quinidine, procainamide, phenothiazines, tricyclic antidepressants) or with hypothermia, cerebrovascular disease, neck surgery. The overall mortality of untreated symptomatic patients is high. If abnormally long QT interval is observed, contributing factors should be treated and beta-adrenergic receptor antagonists could be used (Schwartz and Wolf, 1978; Moss and Schwartz, 1979).

Heart block

Heart block may be functional (vagal stimulation, administration of drugs including digitalis, quinidine, beta-adrenergic receptor antagonists), but more commonly is organic. Classified in three degrees, blocks range from slowing of atrioventricular conduction (1st degree) to complete atrioventricular dissociation (3rd degree). The 2nd degree heart block is subdivided into Möbitz I, (or Wenckebach) type, characterized by progressive lengthening of the PR interval, and Möbitz II type characterized by regularly spaced missing ventricular contractions whilst the PR interval is constant. In this block, the lesion is situated below the A–V node and evolution into complete heart block is expected (fig. 3).

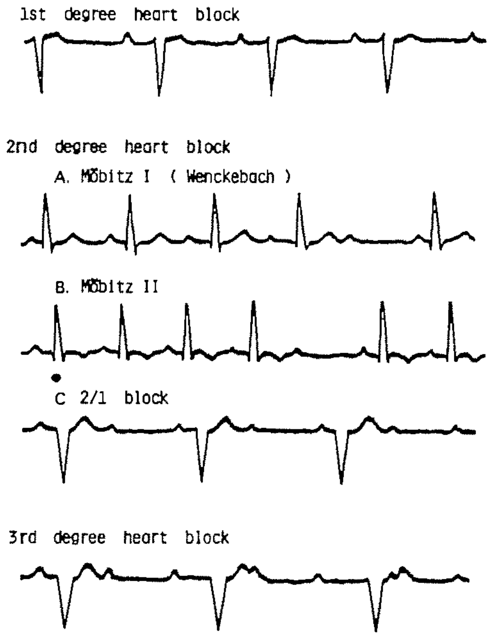

FIG. 3. Electrocardiographic appearances of the various forms of heart block.

Bifascicular blocks are intraventricular conduction defects that may evolve into complete heart block. The bundle of His can be divided into three fascicles: right bundle branch, left anterior fascicle of the left bundle branch and left posterior fascicle of the left bundle branch. Complete left bundle branch block is, by definition, bifascicular. Right bundle branch block may be monofascicular or bifascicular if either left anterior or left posterior fascicles of the left bundle branch are also involved. When right bundle branch block is associated with left anterior fascicle block, the electrical axis shows an axial deviation of −75° or greater; involvement of the left posterior fascicle causes an axial deviation of greater than 110° (fig. 4).

Sick sinus syndrome represents a group of disturbances resulting from failure of normal impulse formation in the sino–atrial node. Severe bradycardia, sinus arrest, paroxysmal or chronic atrial fibrillation and tachycardia appear to alternate. Heart block and life-threatening tachycardia may develop.

Anaesthesia may precipitate the development of complete heart block with very slow ventricular rate in patients with conduction disorders. There are several contributing factors to worsening of conduction. Anaesthetic agents may reduce A–V conduction. Anaesthesia often causes arrhythmias and premature beats are known to facilitate the development of blocks. Alterations of potassium concentration (hypocapnic IPPV, blood transfusion) may be induced and will modify cardiac excitability. This is why insertion of a temporary pacemaker is often necessary before elective or emergency surgery (Wynands, 1976; Simon, 1977; Zaidan, 1979). The indication for temporary pacing is almost absolute for 3rd degree and Möbitz type II blocks. In other blocks (1st degree, 1st degree and left bundle branch block, Möbitz type I, bifascicular blocks) the indication for temporary pacing is imperative if patients have presented Stokes–Adams attacks or unexplained fainting or blackouts. Temporary pacing is also indicated in case of severe bradycardia accompanied by cardiac failure, angina or syncope, in case of atrial fibrillation with very slow ventricular rate and in case of sick sinus syndrome. Without pacing, treatment of tachyarrhythmias caused by sick sinus syndrome is difficult and may result in complete heart block. As stressed by Ponka (1977) failure to use a pacemaker when indicated will cause fatalities.

CONGESTIVE HEART FAILURE

Left or right ventricular failure, even in their early phases, are major factors of cardiac risks of anaesthesia and surgery (Goldman et al., 1977). Diagnosis and treatment of heart failure are essential before surgery. In an emergency this may necessitate i.v. digitalis and administration of diuretics. The clinical presentation of heart failure depends upon which ventricle is most affected.

In left ventricular failure, pulmonary congestion predominates and its symptoms are dyspnoea, orthopnoea and paroxysmal noctural dyspnoea. Interstitial oedema stimulates juxtacapillary J receptors and this causes a pattern of

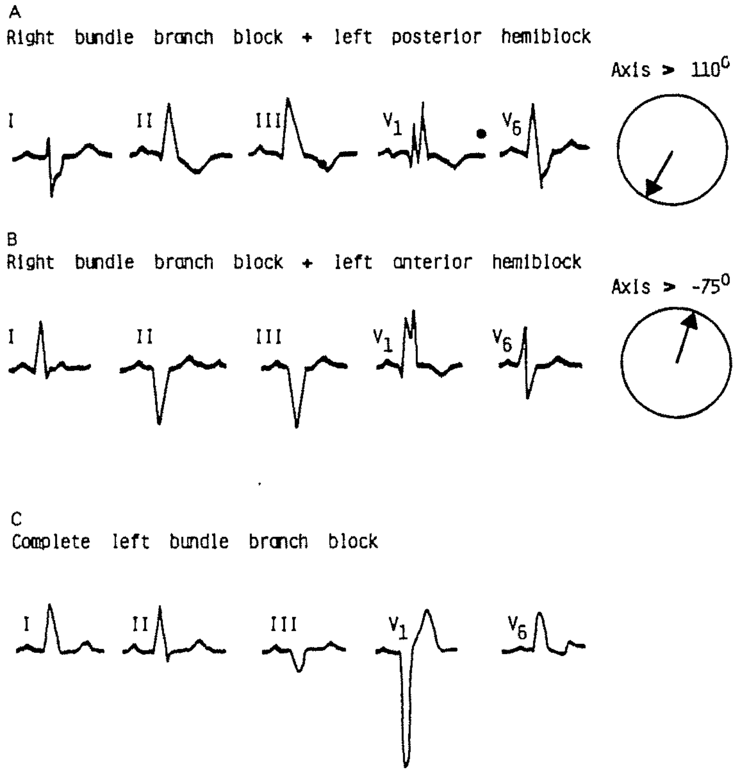
A
Right bundle branch block + left posterior hemiblock
Axis > 110°
I
II
III
V_1
V_6
B
Right bundle branch block + left anterior hemiblock
Axis > -75°
I
II
III
V_1
V_6
C
Complete left bundle branch block
I
II
III
V_1
V_6

FIG. 4. Electrocardiographic appearances of bifascicular block. Bifascicular blocks include right bundle branch block associated with left posterior hemiblock (A), right bundle branch block associated with left anterior hemiblock (B), and complete left bundle branch block (C).

shallow breathing. The increased effort of breathing results in the sense of shortness of breath. Augmented venous return on lying increases the interstitial oedema and explains the orthopnoea. Development of bronchial oedema explains the intense wheezing of some patients. More difficult to recognize are the early signs of left ventricular failure: coughing on assuming the recumbent position, insomnia and nocturia (in the absence of urinary infection), unexplained permanent tachycardia. Physical examination will usually reveal tachycardia, enlargement of the heart and, if the left ventricle is dilated, the systolic murmur of functional mitral incompetence. An early diastolic heart sound (S_3) is heard. Pulsus alternans (alternation of strong and weak beats while the rhythm is normal) is indicative of severe mechanical failure. Basal rales reveal the accumulation of fluid in alveoli and terminal bronchioles. There is no characteristic electrocardiographic pattern of left ventricular failure; the e.c.g. abnormalities reflect atrial or ventricular hypertrophy, myocardial ischaemia or infarction, conduction disorders or dysrhythmias. Chest x-ray reveals an enlarged heart shadow, exaggerated apical pulmonary vessels and prominent septal lines (Kerley's B lines) as a result of basal interstitial oedema and distension of lymphatics.

When right ventricular failure predominates, transsudation of fluid occurs in the systemic rather than the pulmonary circulation. Hepatic congestion is a prominent feature, revealed by abdominal discomfort in the right upper quadrant. The jugular veins are distended, the liver is enlarged and hepatojugular reflux is present. Peripheral pitting oedema is observed. The electrocardiogram may reveal signs of right ventricular hypertrophy and strain or signs of pulmonary embolism (S_1, Q_3, right bundle branch block).

In the light of Goldman's study of the factors of risk, increased jugular venous pressure (indicating right ventricular failure) or early diastolic third heart sound (left ventricular failure) are important indicators of increased cardiac risk.

The repercussions of left ventricular failure on the pulmonary circulation and on right ventricular function are well recognized. However, only recently has the effect of acute right ventricular failure on left ventricular function been studied (Laver, Strauss and Pohost, 1979). In patients with acute respiratory failure, the combination of hypoxaemia, intermittent positive ventilation and positive end-expiratory pressure can increase resistance or impedance to right ventricular ejection. The failing right ventricle dilates and, because the pericardium has limited compliance, the volume that can be occupied by the left ventricle during diastole is reduced and consequently cardiac output may decrease. This must be borne in mind in the assessment of patients with acute respiratory failure and heart disease.

DRUG THERAPY

Digitalis

Administration of digitalis before operation has been advocated to minimize the effects of anaesthetic agents on the myocardium, particularly in patients with previous history of heart failure, left or right ventricular hypertrophy, coronary artery disease, valvular disease, and in patients undergoing cardiac or major pulmonary surgery (Deutsch and Dalen, 1969; Friedlander, 1973). Other authors, however, consider that only heart failure, fast atrial fibrillation or frequent atrial premature beats justify preoperative digitalis (Shelby, 1967). Prevention of arrhythmias by use of digitalis before operation has been advocated in order to minimize the risk of fast supraventricular arrhythmias (Johnson et al., 1976). While Johnson and his colleagues observed a reduction of the frequency of supraventricular arrhythmias (including atrial fibrillation) where digitalis had been administered, other authors have found the frequency of arrhythmias either unchanged (Rose, Glassman and Spencer, 1975) or increased (Tyras et al., 1979). The risk of digitalis-induced arrhythmias is increased by hypokalaemia and by metabolic alkalosis (Brater and Morelli, 1977). Laver and Lowenstein (1980) have summarized their approach as follows:

(1) acute use of digitalis is indicated in case of heart failure;

(2) digitalis is best continued until the evening before operation if the patient with chronic atrial fibrillation has a ventricular rate faster than 80 beat min^{-1} unless digitalis intoxication is suspected;

(3) use of digitalis before operation may be considered before abdominal or intrathoracic operations in patients with previous myocardial infarction and abnormal ventricular function;

(4) digitalis should not be started only for the purpose of counteracting the cardiac depression caused by anaesthetic drugs.

Beta-adrenoceptor antagonists

The adverse consequences of sudden withdrawal of adrenergic beta-receptor antagonists have been well documented. They range from worsening of angina to myocardial infarction and sudden death (Slome, 1973; Alderman et al., 1974). Discontinuation of beta-receptor antagonists 24–48 h before operation makes the circulation more unstable and increases the risk of arrhythmias and of hypertensive crises, which in turn have a detrimental effect on the balance of oxygen demand and oxygen supply (Slogoff, Keats and Ott, 1978). Maintenance of adrenergic beta-receptor blockade throughout the period of operation is beneficial for patients submitting for cardiac or non-cardiac surgery (Prys-Roberts et al., 1973; Boudoulas et al., 1979; Manners and Walters, 1979; Oka et al., 1980). However, the choice of the anaesthetic agent is important. Agents provoking increases of sympathetic activity (cyclopropane, diethylether, fluroxene) should be avoided; their negative inotropic action is unmasked by beta-adrenergic receptor blockade. Methoxyflurane and trichloroethylene cause severe myocardial depression in the presence of beta-adrenergic receptor blockade and should also be avoided (Saner et al., 1975; Roberts et al., 1976). An adverse interaction has been observed between enflurane and propranolol (Horan et al., 1977a), but not between enflurane and oxprenolol (Cutfield et al., 1981). Clinical observations suggest that enflurane may be used to supplement nitrous oxide anaesthesia in the presence of beta-adrenergic receptor blockade (Kaplan and Dunbar, 1976). There is no indication of adverse interactions between beta-receptor antagonists and halothane, isoflurane or opiates supplementing nitrous oxide anaesthesia (Prys-Roberts et al., 1973; Horan et al., 1977b; Prys-Roberts, 1979). Beta-adrenergic receptor antagonists protect the myocardium by reducing the frequency and severity of tachycardia and hypertension. They also protect myocardial function. While they are known to decrease the extent of ischaemic dysfunction after coronary occlusion in experimental animals (Theroux et al., 1976; Vatner et al., 1977) and in man (Norris et al., 1978; Yusuf et al., 1980), they seem to minimize the adverse effect of anaesthesia on the ischaemic myocardium (Cutfield et al., 1981). They play an important role in the safe anaesthetic management of patients with coronary artery disease and arterial hypertension.

The possible hazards of beta-receptor blockade should not be ignored. In patients with cardiac failure, disorders of atrioventricular conduction, asthma or anaemia, beta-receptor blockade may be contraindicated. In the presence of beta-receptor blockade, hypercapnia is likely to cause circulatory depression: the direct negative inotropic effect of carbon dioxide is unmasked. Bradycardia may occur at the time neuromuscular blockade is reversed with neostigmine, particularly if patients are on large doses of beta-adrenergic receptor antagonists (Prys-Roberts, 1979).

OVERALL ASSESSMENT OF RISK

Careful preoperative assessment makes it possible, not only to establish the diagnosis and to evaluate the severity of cardiovascular disease, but also to gain some insight into the risk of cardiac morbidity and mortality. While the classification of physical status according to the Americal Society of Anesthesiologists and the classification of heart disease according to the New York Heart Association are useful, they do not allow the anaesthetist to attach a predictive value to symptoms and signs of heart disease. Using discriminant analysis, Goldman and his colleagues (1977) have been able to identify factors that contribute significantly to the cardiac risk of anaesthesia (table II). The relative importance of each factor has been determined and with the resulting multifactorial index, more than 80% of cardiac outcomes have been predicted. All these factors are easily identified during the preoperative visit and it is easy to see the escalation of risk when several abnormalities are present.

The high frequency of life-threatening complications of anaesthesia and surgery in patients with cardiovascular diseases can be overlooked. Very often anaesthesia and the phase immediately after operation appear to be uneventful and cardiac complications occur over the first few days after operation. Anaesthesia, surgery and responses to stress all contribute to these complications, but thorough assessment before operation is essential to minimize their frequency.

TABLE II. *Multifactorial index of cardiac risk (After Goldman et al., 1977)*

Risk factor	Points
S_3 gallop, increased jugular venous pressure	11
Previous myocardial infarction (6 months)	10
Premature ventricular ectopics (5 per min)	7
Atrial arrhythmias, rhythm other than sinus	7
Age greater than 70 yr	5
Emergency operation	4
Severe aortic stenosis	3
Poor general condition	3
Intraperitoneal or intrathoracic operation	3

Points	Life-threatening complications (%)	Cardiac deaths (%)
0–5	0.7	0.2
6–12	5	2
13–25	11	2
26	22	56

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ANAESTHETIC MANAGEMENT OF CEREBROVASCULAR DISEASE

E. A. M. FROST

The increased use of the operating microscope combined with newer radiological techniques which have greatly improved early and precise diagnosis of intracranial disease mean that many more neurovascular procedures can be undertaken. As vascular disease is rarely restricted to the cerebral circulation, these patients frequently present with disease in many systems and are receiving a variety of drugs.

Cerebral circulation and metabolism are responsive both to systemic physiological alterations and to all anaesthetic agents and techniques. The consequences to cerebral function may be catastrophic if spontaneous or induced changes are inappropriate to the brain's nutritional needs. To provide optimal protection to the brain during stress, the anaesthetist must appreciate both normal cerebral circulation and the consequences of cerebrovascular disease.

ANATOMY

The blood supply to the brain is from the carotid and vertebral arteries. The venous drainage is by a superficial and deep system.

The left carotid and left subclavian arteries are direct branches of the aortic arch. The subclavian arteries each give origin to the vertebral arteries. The right carotid artery and the right subclavian artery arise from the innominate branch of the aorta. Each common carotid artery divides at the level of the 4th cervical vertebra into the internal and external carotid arteries. The external carotid artery supplies the glands, muscles and bones of the head and face and the dura mater.

The internal carotid artery enters the skull through the foramen lacerum and carotid canal and crosses the cavernous sinus. Ophthalmic, posterior communicating and anterior choroidal branches are given off before it terminates on the basal surface of the brain by dividing into the anterior and middle cerebral arteries (fig. 1).

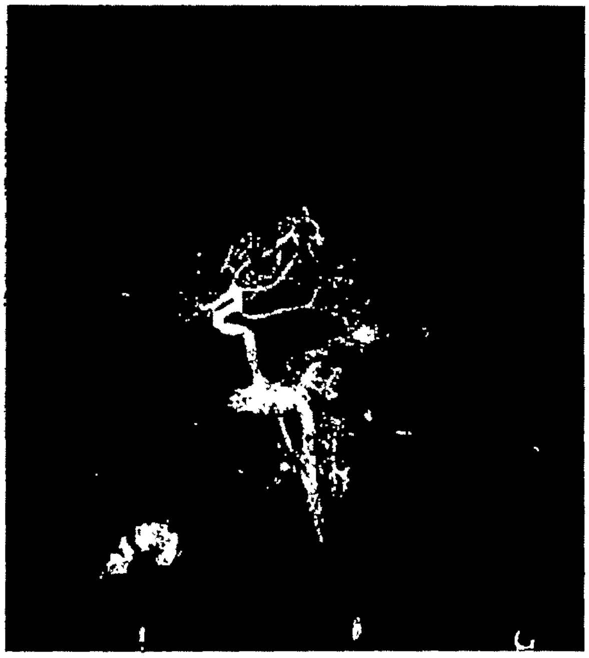

FIG. 1. Lateral view of angiogram demonstrating both middle cerebral (↓) and anterior cerebral arteries (↘) after they arise from the internal carotid artery (←). The posterior cerebral artery (↖) supplies the medial inferior surface of the cerebral hemisphere including the temporal and occipital lobes.

The larger left vertebral and the smaller right vertebral arteries enter the foramen transversarium of C6 on either side and ascend through the neck to C1, where they cross the dura to the anterolateral surface of the upper cervical spinal cord. The vertebral arteries give origin to the posterior inferior cerebellar arteries and rami for the common midline anterior spinal artery which supplies the anterior two-thirds of the spinal cord before joining the midline to form the basilar artery. Paired branches of this common vessel include the anterior inferior cerebellar arteries, the tegmental perforating branches, the superior cerebellar arteries and the terminal posterior cerebral arteries.

Several anastomotic pathways between the arterial systems exist to maintain flow in the face of

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occlusive vascular disease. The circle of Willis connects the left and right carotid circulations and the carotid and vertebrobasilar circulations. Retrograde flow from maxillary ophthalmic arteries can fill the internal carotid artery. Emissary channels connect scalp, bony and dural arteries through petrotympanic branches to the internal carotid artery.

Cortical veins drain into the veins of Trolard and Labbé laterally and inferiorly and into the superior sagittal sinus medially and superiorly. Drainage from the deep grey nuclei passes along periependymal veins to the basal veins of Rosenthal and the vein of Galen to the straight sinus and torcular and hence to the superior sagittal sinus. Lateral sinuses carry venous blood to the sigmoid sinus and internal jugular veins which empty into the superior vena cava. From the posterior fossa, drainage is to cerebellar and basilar plexi into the sigmoid sinus.

PHYSIOLOGY

The brain lacks phosphorylase and glycogen and therefore its metabolism requires a continuous supply of glucose and oxygen. A relatively high blood flow is necessary—approximately 750 ml min^{-1}—and is maintained as long as autoregulatory mechanisms remain intact. Ninety per cent of the cerebral blood flow is supplied through the carotid arteries and 10% through vertebral arteries. Normal values for other metabolic rates are listed in table I. Physiological control of the cerebral circulation is maintained by a precise interaction of myogenic, metabolic, chemical and neurogenic vascular responses.

Myogenic. An important aspect of the cerebral circulation is autoregulation of flow near a constant value, despite changes in arterial perfusion pressure between 60 and 180 mm Hg. The sigmoid shape of this curve predicts that breakthrough of autoregulation will occur above an upper limit of 180 mm Hg mean pressure, and failure of autoregulation will occur as the perfusion pressures decrease to less than 60 mm Hg pressure, as shown in dog studies (Harper, 1965). The exact mechanism for this control is not completely understood, although sympathetic innervation of arteries down to 50–60 µm calibre has been found—a finding which is probably of important clinical significance under pathological circumstances. It is also accepted that the controlling mechanism is sensitive to changes in transmural pressure or the pressure difference between the lumen and the outside of the artery (Keuskamp and Fein, 1977).

Autoregulation is easily abolished by trauma (especially hypoxia), anaesthetic agents (Miletich, Ivankovich and Albrecht, 1976), seizure states, chronic hypertension (Strandgaard, Olesen and Skinhøj, 1973) and diabetes (Bentsen, Larsen and Lassen, 1975).

Metabolic. There is a close relationship between blood flow and the level of oxidative metabolism in brain tissue. A higher rate of flow is found in grey matter, where there is a particularly heavy concentration of mitochondria within the dendrites. There are also phasic variations in the blood flow

TABLE I. *Normal values for metabolic rates of consumption of cerebral nutrients.* **Defined as mean systemic arterial pressure minus mean cerebral venous pressure or mean systemic arterial pressure minus intracranial pressure*

Full name	Abbreviation	Normal values and units
Cerebral blood flow	c.b.f.	0.44 ml g^{-1} min
Regional cerebral blood flow	r.c.b.f.	0.2–0.8 ml g^{-1} min
Cerebral perfusion pressure*	CPP	80 mm Hg
Cerebrovascular resistance	CVR	0.24 kPa ml^{-1} min^{-1} per 100 g
Arteriovenous oxygen content difference	$(Ca_{O_2} - Cv_{O_2})$	0.068 ml ml^{-1}
Cerebral metabolic rate for oxygen	$CMRo_2$	0.03 ml g^{-1} min
Cerebral metabolic rate for glucose	$CMR_{glucose}$	0.045 mg g^{-1} min
Cerebral metabolic rate for lactate	$CMR_{lactate}$	0.023 mg g^{-1} min
Cerebral venous oxygen tension	Pv_{O_2}	4.7–5.4 kPa
Oxygen glucose index	OGI	90–100%
Lactate glucose index	LGI	0–10%
Cerebral blood flow equivalent	$CBF . CMRo_2^{-1}$	14–15 ml blood per ml O_2

which may be associated with increased electrophysiological activity such as seizures, evoked potentials or steady potential shifts (Brierley, 1973).

As metabolic rate increases or the relative supply of oxygen within small areas of the brain decreases, release of local metabolites results in vasodilatation. An increase in tissue hydrogen ion concentration, rather than a decrease in oxygen, is considered the major metabolic factor coupling flow and metabolism. Alteration of serum Ca^{2+} and K^+ concentrations, changes in carbonic anhydrase activity and probably also changing ADP concentrations, also influence local flow.

Chemical. Hypercarbia secondary to respiratory insufficiency causes cerebrospinal fluid and brain tissue acidosis. Within a range of 2.7–8 kPa, c.b.f. varies almost linearly with Pa_{CO_2}. Unit change (0.133 kPa or 1 mm Hg) in Pa_{CO_2} is associated with a change in c.b.f. of about 0.02 ml g^{-1} min and a change in cerebral blood volume of about 0.0004 ml g^{-1}. Within the same range, Pa_{CO_2} has no apparent effect on $CMRo_2$. Alteration of c.b.f. by changing Pa_{CO_2} occurs almost immediately as carbon dioxide diffuses rapidly from blood vessels to affect the pH of extracellular fluid. If Pa_{CO_2} is kept constant and only arterial H^+ or HCO_3^- altered, little immediate change is seen in c.b.f. as these ions enter the extracellular fluid space more slowly.

The decrease in c.b.f. with hypocarbia is limited and minimal flow is reached at about 1.3–2.6 kPa, when cerebral tissue hypoxia may prevent further reduction in flow.

Decreasing Pa_{O_2} with normal Pa_{CO_2} does not affect c.b.f. until Pa_{O_2} decreases to less than 6.5 kPa, at which point cerebral vasodilatation occurs and c.b.f. increases.

Neurogenic. Both adrenergic and cholinergic nerves innervate extra- and intracranial blood vessels. Stimulation of nerves can markedly affect the calibre of pial vessels. However, the responses of these pial vessels to hypoxia, hypercapnia and hypertension appear to be similar whether the nervous pathways are intact or not. Morphological and histological studies indicate that the nerve plexuses on cerebral vessels are identical to those in other vascular beds, but other studies conclude that the nerve actions are small or non-existent (Kuschinsky and Wahl, 1978; Purves, 1978). Probably, neurogenic control is not of major significance under normal circumstances, but becomes important under stress states such as hypovolaemic shock.

Measurement of c.b.f.

Non-invasive techniques are now available for the quantitative assessment of regional cerebral blood flow and metabolism. The most practical systems monitor the washout of the isotope xenon-133 from small regions of the brain. Xenon-133 is administered by inhalation until saturation of the brain is achieved, at which time the isotope is in equilibrium between blood and brain and its washout rate will therefore be limited as a function of the blood flow rate. The blood flow rate can be measured externally by up to 250 scintillation crystals, each of which looks at a small cylinder of brain tissue (Lassen, Ingvar and Skinhøj, 1978). In centres with access to a cyclotron, it is now also possible to measure the metabolic rates for carbon dioxide generation, ammonia turnover, oxygen consumption and local cerebral blood volume in small regions of cerebral tissue using positron emitting radioisotopes imaged on tomographic scanners.

PATHOPHYSIOLOGY

Anaesthetic management of patients with neurovascular disease must be aimed at protection against the development of ischaemic infarction, at optimizing conditions which will favour resolution of ischaemia and the maintenance of normal intracranial dynamics. Factors which decrease substrate supply or increase metabolic demand increase the risk of infarction. Factors which augment blood flow or decrease metabolism, decrease the chance of infarction. The degree of ischaemia necessary to produce a clinical deficit is unknown, but e.e.g. slowing is seen at c.b.f. values of 0.2 ml g^{-1} min^{-1}. Flow rates are decreased by systemic hypotension and by focal vascular occlusion. Sickle cell disease and paraproteinaemia increase cerebrovascular resistance and decrease flow. Brain oedema and hydrocephalus increase the critical closing pressure of the capillary system. Haematomas cause a mass effect and decrease perfusion pressure at the point of focal compression, with reactive oedema and hyperaemia in the surrounding brain.

Hypoxia which may result from respiratory or central causes results in a relative shift from oxidative metabolism within mitochondria to anaerobic, largely extramitochondrial, glycolysis with conversion of pyruvate to lactate. Early structural changes in the mitochondria (Brierley, 1973) occur with failure of presynaptic activity (Williams and Grossman, 1970). As the intra- and extracellular lactate concentrations increase, there is a decrease in the rate of production of ATP by oxidative phosphorylation. Loss of this high-energy phosphate causes loss of ATP-activated cation transport with aberrations of neuronal membrane resting potentials. The blood–brain barrier, which restricts permeability, breaks down with injury to endothelial cells of the capillaries. Glial processes around the capillaries are then altered, which interferes with transport functions of the glia and eventually cerebral oedema results. Oedema aggravates ischaemia by increasing critical closing pressure. A vicious cycle of ischaemia and oedema may then lead to irreversible infarction.

Therapy at several points may interfere with this sequence of events by augmenting blood flow, decreasing oedema formation or reducing metabolic demands. Adaptation of anaesthetic techniques may, in many instances, be utilized to maintain or decrease cerebral blood flow or exert a protective effect on the brain by reducing the metabolic rate of oxygen utilization.

THE MAJOR CEREBROVASCULAR DISEASE ENTITIES

Thromboembolic disease

Ischaemic and haemorrhagic variants of cerebrovascular disease are the third leading cause of death in the Western world. Approximately 78% of new "strokes" are caused by thromboembolism, with the remainder related to haemorrhagic causes such as hypertensive intracerebral haemorrhage, aneurysmal haemorrhage, rupture and haemorrhage from an arteriovenous malformation and miscellaneous other causes such as vasculopathies and coagulopathies.

Thromboembolic syndromes are classified in terms of the duration and severity of the clinical deficit. Transient ischaemic attacks (TIA) are characterized by deficits which persist for less than 24 h and resolve completely. The reversible ischaemic neurological deficit (RIND) persists for longer than 24 h and resolves within 1 week. The progressive stroke (PS) is the most unstable condition and is characterized by worsening of the deficit with serial observation. The complete stroke (CS) describes a persistent deficit which may be minor or disabling.

A series of non-invasive tests has been developed to evaluate and screen patients with cerebrovascular disease. These include ophthalmodynamometry, assessment of flow reversal in the ophthalmic–facial collaterals with directional Doppler equipment, thermography and oculoplethysmography (Fein, 1978). Plain skull and cervical x-rays may disclose calcification in the cervical or siphon portions of the internal carotid arteries. CT scan may be useful in quantitating the volume of infarction, but the scan usually becomes positive only 24–48 h after the stroke. Contrast enhancement in the periphery of an infarction represents the hyperaemia of adjacent brain tissue.

Aneurysms; arterio–venous malformations

Subarachnoid haemorrhage as a result of rupture of an intracranial aneurysm has an immediate mortality of 43%. With conservative management, 35% of survivors will die following another bleed within 1 year and 51% will be dead within 5 years. The mortality rate is greater after recurrent haemorrhage—64% after the first re-bleed and 96% after the second. Neurological deficit occurs in 30% of survivors (Adams, Loach and O'Laoire, 1976).

Contrary to previous belief, it has been suggested that this is an acquired rather than a congenital disease. Evidence for this is based on the fact that aneurysms are rarely found in autopsy of infant brains, and on a clinical association between aneurysms and angiographically visible atheromata which form on the internal elastic lamina (Bell and Symon, 1979).

Arteriovenous malformations (AVM) may occur anywhere within the central nervous system and commonly affect younger age groups. Spinal cord AVM are usually surface lesions which occur one-tenth as frequently as cerebral AVM. The former are more likely to present with progressive myelopathy than with haemorrhage. Selective angiography reveals the arterial supply and extent of the lesion. Dorsally located malformations are operable and often require extensive laminectomy. The lesion is stripped off the cord with microsurgical technique, and it is reasonable to expect some resolution of neurological deficit.

Hypertensive intracerebral haematoma

Hypertensive intracerebral haematoma occurs in the fifth and sixth decades and is related to fibrinoid degeneration of the medium-sized thalamostriate arteries supplying the basal ganglia. In this location, haemorrhages are often catastrophic. Intracranial hypertension is often life-threatening and requires immediate attention, including ventilatory assistance. A significant portion of haematoma may be placed more laterally or in a cerebellar hemisphere. In such cases evacuation of the clot with open craniotomy may be life-saving. Surgery of the comatose patient with a deeply placed haematoma is often heroic; however, such lesions may now be treated more reasonably by stereotaxic aspiration.

Hypertensive encephalopathy

The severity of this complication of hypertension is directly related to the arterial pressure. The syndrome is associated with some neurological impairment and increased intracranial pressure. The diagnosis may be confirmed by a good clinical response to antihypertensive agents.

ANAESTHETIC EVALUATION BEFORE OPERATION

Multisystem disease

The majority of patients with cerebrovascular disease are also hypertensive and thus two problems arise. First, the hypertensive patient subjected to general anaesthesia is at increased risk of myocardial infarction. Second, hypertensive patients may be particularly unstable during the anaesthetic period, becoming hypotensive during operation and further compromising an ischaemic area of brain. After operation, hypertension may develop, putting atheromatous cerebral vessels at risk of rupture.

In several studies of small groups of hypertensive patients Foëx and Prys-Roberts (1974) concluded that patients with untreated or inadequately treated hypertension were at greater risk of arterial hypotension during anaesthesia and of associated myocardial and cerebral ischaemia. They recommended that patients with untreated hypertension should have their arterial pressure brought under control before being subjected to anaesthesia.

In a more recent prospective study, Goldman and his colleagues (1977) determined that elective surgery in the absence of ideal antihypertensive therapy need not subject patients to an added clinical risk, provided that the diastolic pressure is stable and not greater than 110 mm Hg, and that close monitoring and prompt therapy avoids hypo- or hypertensive episodes during or after operation. A strong correlation between carotid occlusion and hypertension before operation (independent of recent or distant preoperative arterial pressure readings and of cardiovascular complications of hypertension) has been reported (Goldman et al., 1978).

Cerebral ischaemia usually does not manifest itself as neurological deficit until carotid artery stenosis reaches about 80% or plaque embolization has occurred. In addition, the disease is bilateral in about 50% of cases. Abnormalities of the circle of Willis—usually hypoplastic communicating vessels—are found in the majority of cases and further decrease the ability to augment contralateral flow. Thus the margin of safety is greatly reduced, and relatively small decreases in systemic arterial pressure or decreases in cerebral vessel diameter may precipitate a catastrophic situation. Preoperative evaluation of patients with carotid artery disease should include a test of neck motion to ascertain that consciousness is maintained with lateral movement.

In our study of 80 patients presenting for cerebral revascularization techniques (Frost et al., 1980) evaluation before surgery revealed hypertension in 48, previous history of myocardial infarction in 21 and diabetes mellitus requiring insulin therapy in 18. In addition we found a close correlation between atheromatous disease and heavy smoking (40% of the patients had smoked more than 40 cigarettes daily for more than 20 years). Bell and Symon (1979) noted a similar association between smoking and subarachnoid haemorrhage.

Chronic lung pathology with decreased arterial oxygen saturation and increased carbon dioxide retention, therefore, is commonly found in these patients. Because of the importance of maintenance of normality of blood-gas tensions, careful monitoring and consequent adjustment of respiratory oxygen concentration and ventilatory parameters is imperative.

It is, however, just as important to avoid hyperventilation under anaesthesia, which may cause demonstrable cerebral damage as determined by a critical flicker fusion or reaction time test (Allen and Morris, 1962; Wollman and Orkin, 1968). Possibly, hyperventilation constitutes an additive and adverse effect to the patient who already has neurological damage which may be related to the decrease in cortical $P\text{O}_2$ which parallels the decrease in Pa_{CO_2} as cerebral vasoconstriction increases. An anaesthetic technique in patients with stroke should therefore be aimed at adequate ventilation without decrease in Pa_{CO_2} to less than 4.8 KPa.

Hyperkalaemia following suxamethonium is a recognized danger in patients with central nervous system lesions with skeletal muscle paralysis (Tobey et al., 1972). The phenomenon may occur in patients with both upper and lower motor neurone lesions. Increased serum potassium concentrations are found in the venous blood from all paralysed mucles for several weeks after injury, indicating that the source of the potassium is the abnormal muscle distal to the neural lesion. The subsequent administration of suxamethonium may increase serum potassium concentrations and cause cardiac arrhythmias or even arrest. It is therefore imperative that preoperative serum potassium concentrations are known and within normal limits; the patient is pretreated with small doses of a non-depolarizing muscle relaxant, and suxamethonium is avoided or used only in minimal amounts.

Multiple pharmacological regimens

Approximately 85% of patients with cerebrovascular disease are being prescribed several drugs on a long-term basis. Most commonly, these include digitalis preparations, diuretics, antihypertensives, antiarrhythmics, anticoagulants, insulin and steroid preparations.

It is generally agreed that, when patients are receiving antihypertensive or antiarrhythmic medication before anaesthesia, it is advisable for that medication to be continued up to and including the day of operation as this will minimize the likelihood of hypertension after operation.

Patients with persistent increased arterial pressures receiving combinations of drugs and those with histories of cerebral, myocardial or renal disease constitute a very high risk group. These patients can be identified by the criteria in Goldman's multifactorial risk index (Goldman et al., 1977), which establishes a useful means of selection of patients suitable for anaesthesia, but is of little help in determining proper intraoperative and postoperative management of these patients.

Although surgery is frequently delayed pending radiological diagnosis or resolution of spasm following subarachnoid haemorrhage (Adams, Loach and O'Laoire, 1976), monitoring of serum electrolyte balance must be maintained. Preoperative preparation of patients with ruptured intracranial aneurysms includes bed rest with control of hypertension and infusions of aminocaproic acid, which is an antifibrinolytic agent used to preserve clot formation (Ransohoff, Goodgold and Benjamin, 1972). As this therapeutic regimen predisposes to deep venous thrombosis and pulmonary embolism, passive physiotherapy and bedside respiratory function tests should be maintained daily.

Aspirin, usually given for several weeks before surgery to prolong clotting times in patients at risk of stroke, may decrease essential coagulation factors (especially factor X). A clotting profile is essential on the day before surgery.

Patients receiving long-acting insulin preparations should be stabilized on soluble insulin before operation.

Premedication

Atropine i.m. should be avoided because of the tachycardia and unpleasant drying effects. It is preferable to give small doses of a tranquillizer such as diazepam 5–10 mg orally about 90 min before surgery.

ANAESTHETIC MANAGEMENT DURING OPERATION

Carotid endarterectomy

The major features of anaesthetic management of patients presenting for carotid endarterectomy are listed in table II.

Probably the most accurate assessment of adequate cerebral blood flow is obtained by maintaining voice contact with the patient during operation and utilizing a regional cervical plexus block technique (Rich and Hobson, 1975). However, such a technique causes anxiety and some pain, resulting in tachycardia, hypertension, hypercarbia (rebreathing under drapes) and increased myocardial and brain oxygen consumption. In addition neurological damage may not occur immediately after carotid artery clamping and may even be delayed for up to 30 min, occurring at a time when surgical attention may be directed elsewhere.

In the well-informed patient without other systemic disease, regional anaesthesia does have a place. Otherwise, general endotracheal anaesthesia and the control of ventilation which it affords, in combination with continuous e.e.g. monitoring, should be used.

TABLE II. *Carotid endarterectomy: main categories which should be observed in the anaesthetic management of the patient undergoing carotid artery surgery*

- (1) Careful preoperative history
  - (a) Assessment of multisystem disease
  - (b) Optimal medical condition
  - (c) Continue cardiovascular therapeutic regimen
- (2) Maintain cerebral perfusion
  - (a) Avoid hypotension and bradycardia
  - (b) Normocarbia
  - (c) Surgical shunt
- (3) Anaesthetic agent to decrease CMRo_2
- (4) Monitoring
  - (a) E.c.g.
  - (b) Arterial cannula
  - (c) E.e.g.
  - (d) Stump pressure
  - (e) C.b.f.
- (5) Close observation after operation
  - (a) Maintain normotension
  - (b) Clear airway
  - (c) Neurological assessment

Debate has continued over the merits of hypercarbic or hypocarbic states during anaesthesia for carotid endarterectomy (Wollman, 1970). Cerebral blood flow increases linearly with increase in Pa_{CO_2}. Thus, establishment of hypercarbia, by increasing collateral flow, might be beneficial in cases of carotid artery stenosis. However, ischaemic areas of the brain are probably already maximally dilated as a result of regional autoregulation and a reduction in resistance in non-ischaemic areas may cause blood to flow from ischaemic to normal areas of the brain, causing a condition which has been named a "steal phenomenon". Retained carbon dioxide increases systemic arterial pressure (which is beneficial), but causes a greater frequency of arrhythmias, especially in patients who already have generalized vascular disease. In addition, hypercarbia decreases stump pressure and increases cerebral venous pressure, both of which decrease cerebral perfusion pressure.

Hypocarbia has an opposite effect and increases resistance in non-ischaemic areas which may direct flow to ischaemic areas. However, this may jeopardize healthy brain and increase resistance in collateral vessels supplying ischaemic areas. A shift of the oxygen dissociation curve to the left in respiratory alkalosis makes oxygen less available to tissues. It would seem logical that, if the awake patient is functioning well at normocarbic values, these values should be maintained during operation.

A means of determining adequacy of cerebral function during carotid clamping is essential (Sharbrough, Messick and Sundt, 1973). The cerebral function monitor, which is an electroencephalographic processor giving information essentially from a single pair of parietal electrodes, probably gives only a gross indication of activity. Although stump pressures greater than 50 mm Hg are said to indicate adequate flow, e.e.g. tracings may be definitely flattened at values even greater than this (fig. 2).

Normotension or slight hypertension must be maintained as autoregulatory mechanisms are frequently altered regionally, if not globally. Long-term ingestion of antihypertensive medications frequently makes patients susceptible to hypotensive episodes initially. These changes may be detected immediately if direct arterial pressure recording has been begun immediately before or during induction. Stabilization of arterial pressure is achieved by increasing fluid administration, infusion of a 0.02% phenylephrine hydrochloride solution and use of light planes of anaesthesia.

The question arises as to the use of i.v. or inhalation agents for maintenance of anaesthesia. Barbiturates decrease CMRo_2, but they also decrease c.b.f. In addition, arterial pressure may be difficult to maintain and emergence is frequently delayed. An inhalation agent such as halothane will also decrease CMRo_2, but increase total c.b.f. (which may result in some, but not total, steal effect). Although arterial pressure may decrease initially, emergence from anaesthesia is usually prompt and complete. Thus, low-dose inhalation techniques are probably preferable.

Extracranial–intracranial anastomosis

The technique of microvascular extracranial to intracranial anastomosis was developed to increase collateral blood flow in patients with cerebrovascular insufficiency (Yasargil, 1967). The anastomosis may be performed in the anterior circulation between the superficial temporal artery and a cortical branch of the middle cerebral artery, or posteriorly between the occipital artery and the posterior inferior cerebellar artery. These operations are long, performed under higher magnification and through a narrow exposure. Respiratory and cardiac pulsations are magnified and make microdissection difficult. The major

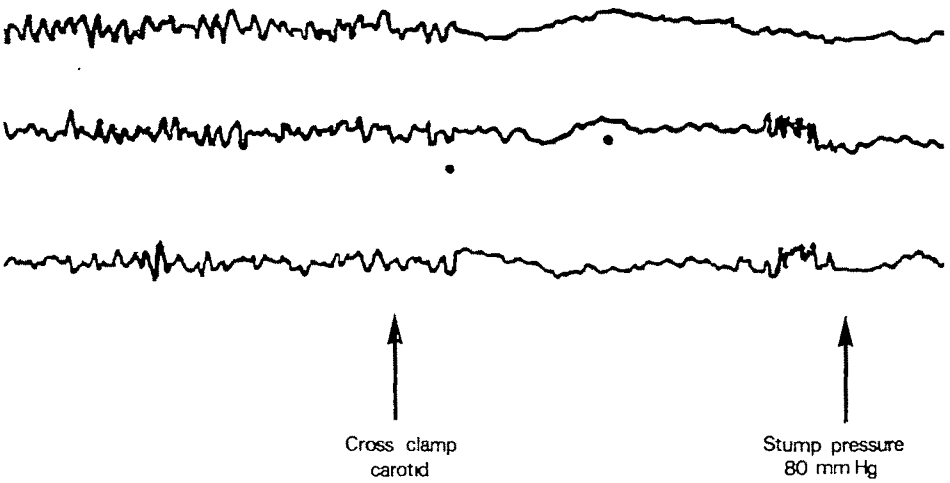

FIG. 2. Definite flattering of e.e.g. pulsations is seen shortly after cross-clamping of the carotid artery in a patient with bilateral carotid artery disease and a mean systemic arterial pressure of 105 mm Hg. The stump pressure is apparently adequate.

requirements, listed in table III, include maintenance of cerebral perfusion pressure without increase in cerebral metabolic demands.

Routine monitoring in all these patients should include continuous temperature recordings and early insertion of an arterial cannula for both arterial blood-gas estimation and arterial pressure measurements. Superficial temporal to middle cerebral artery bypass procedures are performed supine, whereas posterior circulation anastomoses are usually carried out in a sitting position, when all the precautions necessitated by this position must be observed.

TABLE III. *Anaesthetic considerations for extracranial–intracranial anastomosis*

(1) Maintain normocarbia
(2) Maintain cerebral perfusion pressure
(3) Decrease CMR_{O_2}
(4) Reduce brain movement
(5) Administer low molecular weight dextran

The surgical technique involves clamping of a branch of the middle cerebral artery for approximately 1 h. Therefore, an agent such as a barbiturate which may afford ischaemic protection might be preferable (Smith, Hoff and Nielson, 1974). However, this agent causes marked cerebral vasoconstriction which might further decrease collateral flow to ischaemic areas. Low-dose inhalation agents in combination with normocarbia cause both some cerebral vasodilatation and a decrease of cerebral metabolic rate of oxygen consumption. Thus blood flow is maximally maintained to poorly perfused areas.

The absence of the development of any new neurological deficit immediately after operation in our series (Frost et al., 1980), and the ability to perform accurate neurological assessment because of prompt return to consciousness would indicate that this regimen is satisfactory.

Brain movement as a result of cardiac and respiratory action is problematic at high magnification. Use of a head-up position, less acute head turning, smaller tidal volumes with increased respiratory rate and judicious use of small doses of frusemide will all combine to lessen this brain bounce. Although not yet used clinically, a modification of jet ventilation would appear to lend itself to these situations (Kirby, 1980).

Bypass surgery is semi-emergent as it is usually occasioned by increasing frequency of transient ischaemic attacks. Thus the brain may appear swollen and oedematous at surgery. The temptation exists to use hyperventilation techniques to reduce intracranial pressure. However, this manoeuvre is rarely effective as the area involved has usually lost its reactivity to carbon dioxide and the vasoconstriction obtained is deleterious to the collateral supply and to other, marginally supplied areas. The judicious use of osmotic diuretics and c.s.f. drainage are preferable.

Low molecular weight dextran has been shown to maintain flow through freshly anastomosed vessels. It is usually infused at a rate of 50–100 ml h^{-1}. However, in about 50% of patients, persistent oozing of blood or increasing arterial pressure recordings result and this therapy should then be discontinued.

Aneurysm and arteriovenous malformations

Anaesthesia should be induced with thiopentone which constricts cerebral vessels and helps modify the increases in intracranial pressure caused by laryngoscopy (Shapiro et al., 1972). As maintenance of a stable transmural pressure around the aneurysm is of key importance until after successful clipping of the defect, liberal use is made of a laryngotracheal spray of 4% lignocaine to attenuate the hypertensive response to intubation and to prevent bucking during the insertion of the pinhead holder. Pretreatment with lignocaine 1.5 mg kg^{-1} i.v. also has been shown to modify the increases in intracranial pressure associated with these manoeuvres (Bedford et al., 1980). Although sodium nitroprusside has also been used to control arterial pressure during laryngoscopy (Stoelting, 1979), the increase in intracranial pressure which occurs, at least in normocapnic patients, as cerebrovascular resistance decreases, probably offsets any beneficial effects (Turner et al., 1977). Addition of catecholamines to scalp infiltration is avoided as the subsequent absorption of this drug causes hypertension after about 10–20 min (Christensen, Jensen and Søgaard, 1980). Controlled ventilation to maintain Pa_{CO_2} values of 27–30 mm Hg is established almost immediately. Halothane, in a concentration of 1 MAC or less, is most often used. If spinal drainage through a lumbar catheter is used, fluid is allowed to drip out rather than be aspirated—again, to stabilize transmural pressure. Insertion of the saw guide may also increase intracranial pressure (Shapiro et al., 1972) and therefore care must be taken to ensure adequate ventilation and early withdrawal of cerebrospinal fluid. Early establishment of direct arterial pressure recording is essential. Other monitors are listed in table IV. Anaesthesia is probably best maintained with a light inhalation technique which permits prompt return to consciousness after operation and facilitates early neurological examination.

TABLE IV. *Monitors necessary for intracranial aneurysm surgery*

- E.c.g.
- Oesophageal stethoscope
- Urine output
- Inspiratory pressure gauge
- Two large-bore i.v. cannulae
- Arterial cannula with continuous arterial pressure recording
- Ventilator
- Temperature probe
- Drip counter

Several drugs and techniques have been advocated to reduce arterial pressure and thus facilitate dissection around the aneurysm (Yashon, Marquess and Vise, 1975). Sodium nitroprusside (SNP) affords precise control and arterial pressure returns to normal values within 1 min of discontinuing the infusion. If SNP is not started before the surgeon begins to work in the immediate area of the aneurysm or arteriovenous malformation, the total dose rarely exceeds 10–15 mg and duration of administration is generally less than 1 h. Problems with cyanide toxicity are exceedingly rare at these concentrations and tachyphylaxis, tachycardia and failed response—complications encountered in more than 60% of cases receiving trimetaphan—seldom occur. Systemic arterial hypertension has been reported on discontinuation of sodium nitroprusside, probably as a result of persistently increased plasma renin activity (Khambatta, Stone and Khan, 1979). Measures which may be taken to minimize any arterial pressure increase during this critical time after aneurysm clipping include increasing the depth of anaesthesia or judicious use of small doses of frusemide (20 mg i.v.).

Using postoperative angiographic studies of patients who developed new deficit after surgery, we found that patients who received SNP showed less vasospasm than those in whom halothane had been used for hypotension (Frost, Tabaddor and

TABLE V. *Outcome of 126 patients operated on for intravascular aneurysm clipping using three different hypotensive techniques*

Outcome	None	Tri-metaphan	Halothane	SNP
Intact	7 (41%)	7 (41%)	10 (43%)	50 (82%)
New deficit	6 (35%)	7 (41%)	14 (45%)	10 (15%)
Death	4 (24%)	3 (18%)	7 (23%)	1 (2%)
Totals	17	17	31	61

Arancibia, 1979). Table V shows our outcome figures against hypotensive technique in 126 patients operated on at our institution.

Sodium nitroprusside has also been used successfully when neurosurgery has been performed during pregnancy. Careful monitoring of fetal heart rate and uterine activity revealed no abnormalities and apparently healthy babies were subsequently born (Frost, 1980).

It has been observed that during periods of hypotension, intrapulmonary ventilation–perfusion inequalities ($\dot{V}/\dot{Q}$) may increase, particularly if there is pre-existent pulmonary disease (Colley and Cheney, 1977). It has been suggested that this is a result of the ability of the hypotensive agent to overcome the normal compensatory pulmonary vasoconstriction which occurs in response to hypoxia. Reversal to previous values occurs promptly on discontinuing the hypotensive technique. Although there does not appear to be any correlation between the amount of the ventilation–perfusion abnormality which develops and the neurological outcome, patients who are more hypoxic for longer periods of time have an increased number of and more severe respiratory problems after operation. If the estimated shunt is greater than 25%, frank respiratory distress syndrome may develop, necessitating several days of respiratory support after operation.

Patients with pre-existing lung disease may develop more pulmonary abnormalities, and it is prudent to perform arterial blood-gas estimations early in the case to allow for any necessary adjustment of inspired oxygen concentration before the period of hypotension.

Nitroglycerin has also been suggested as a potent hypotensive agent with less potentially toxic effects than SNP (Chestnut et al., 1978). This solution should be freshly prepared, must be protected from light and has an expiry time of 8 h. Hypotension is achieved within 2 min, but there may be considerable further downward drift. Recovery rate is also relatively slow (about 12 min). The total dose of nitroglycerine over a 45-min period is about 12 mg (3 ml). Tachycardia, tachyphylaxis or rebound hypertension are uncommon.

Hypothermia, which substantially increases anaesthetic time, is no longer commonly used during vascular neurosurgery. The technique causes a much greater frequency of arrhythmias during and after surgery and delays return to consciousness.

POSTOPERATIVE CARE

Carotid endarterectomy

Both hypotensive and hypertensive episodes may occur in the period immediately after operation because of reduced baroreflex function. Hypotension reduces perfusion of both the brain and heart and hypertension increases the work and oxygen demand of the myocardium. The end result is likely to be myocardial ischaemia in both instances. The major cause of serious postoperative morbidity in patients undergoing carotid endarterectomy is myocardial infarction. In addition, hypertension may increase capillary hydrostatic pressure, especially in ischaemic areas of the brain, leading to protein leak, oedema or haemorrhagic infarction. Thus maintenance of preoperative baseline arterial pressure after surgery is critical.

Careful monitoring and trend recording in an intensive care unit setting is essential. Antihypotensive medications before operation should be restarted as soon as possible. Hypotension is treated with fluid replacement, ventilation and infusion of 0.02% phenylephrine hydrochloride solution as necessary. Hypertensive episodes, which occur more commonly, require aggressive therapy when mean arterial pressure increases more than 15–20% above baseline recordings.

However, rapid reduction of arterial pressure by more than 25% may in itself cause cerebral ischaemia and therefore therapy must be cautious. Useful drugs for parenteral therapy include labetalol 0.5 $\text{mg kg}^{-1}\,\text{h}^{-1}$ or sodium nitroprusside 70 $\mu\text{g kg}^{-1}\,\text{h}^{-1}$ by slow infusion. Extremely close observation of continuous arterial pressure recordings is mandatory. Other parenteral drugs which may be useful include hydrallazine 5–20 mg i.m. or i.v. or diazoxide in a bolus injection of 50 mg which may be repeated twice. Addition of propranolol 0.5–1 mg given slowly may augment the effects of hydrallazine.

The airway must also be easily accessible and watched for developing intrinsic or extrinsic obstruction such as laryngeal oedema or clot formation. Patients frequently complain of throat pain, which is probably related to retraction on the trachea or oesophagus during operation. Treatment consists of reassurance and topical anaesthetic lozenges.

Finally, frequent evaluation of neurological status is important to monitor for vessel obstruction or embolization which might require surgical re-exploration.

Extracranial–intracranial anastomosis

As these procedures involve only the superficial cortex of the brain, patients should be awake and the trachea extubated on entry to the recovery room.

Again, close observation of all vital signs for a 48–72 h period, including careful, frequent neurological assessment is necessary. Patients with a previous history of myocardial infarction are at particular risk of cardiac complications after operation and attention to maintenance of arterial pressure close to preoperative baseline values is essential. Early ambulation is desirable to decrease embolic phenomena. All previous medications with the exception of aspirin should be restarted as quickly as possible. These patients appear to suffer little pain after operation and thus narcotics and their depressant effects can usually be avoided.

Flap necrosis may occur in the scalp area supplied by the ligated superficial temporal artery and may cause fever or sepsis after surgery.

Aneurysms and arteriovenous malformations

Although these patients are less likely to exhibit cardiovascular instability, intensive monitoring is still essential. Hypertension may develop and indicate vasospasm or clot formation. An associated bradycardia requires prompt CT scanning to exclude an intracranial mass. Currently, postoperative care is aimed at maintaining arterial pressure at slightly greater values by increasing the blood volume.

As the arterial malformation is now clipped and should no longer be at risk of rupture, caveats against coughing or other respiratory manoeuvres need no longer be as stringently applied.

Following fronto–temporal procedures, oedema formation frequently results in the temporary closing of one or other eye, hindering neurological assessment. Again, trend recording of neurological status is essential.

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ANAESTHESIA FOR PATIENTS WITH CORONARY ARTERY DISEASE

J. L. WALLER AND J. A. KAPLAN

Much has been written during the past decade regarding the anaesthetic management of patients with coronary artery disease (CAD). The early literature on this topic focused upon care of patients undergoing cardiopulmonary bypass for surgical correction of their cardiac conditions. However, more recent discussions have turned toward the management, during non-cardiac surgery, of patients whose underlying cardiac disease has not been corrected. This review concerns the latter group of patients.

The goals to be achieved in the management of patients with CAD may be divided into two broad categories: the preservation of myocardial performance (ventricular function), and prevention or treatment of myocardial ischaemia. Accomplishment of these goals is a complex task requiring coordination of anaesthetic care, monitoring and pharmacological intervention.

EVALUATION BEFORE OPERATION

The presence of CAD modifies not only the management of a patient while he is undergoing surgery, but also requires additional steps in preoperative evaluation and preparation for operation. In addition to the information routinely obtained from a medical history and physical examination, the patient's cardiovascular status should be evaluated in considerable detail. Information regarding the anatomical diagnosis, predominant symptoms, the clinical course and complications should be obtained. An effort should be made to quantitate the patient's disability resulting from CAD, in terms of reduced exercise tolerance. The specific date of the most recent myocardial infarctions should be obtained, since Tarhan and others (1972) and Steen, Tinker and Tarhan (1978) have shown a clear relationship between recent infarctions and perioperative mortality. Precise information as to the patient's current drug treatment, the doses and the response to therapy should be noted, with particular attention to digitalis preparations, diuretic, antiarrhythmic and antihypertensive agents, nitrates and beta-adrenoceptor blocking drugs. Data from nursing notes, treatment schedules and other physician's consultations, as well as from haematological, biochemical, radiological and e.c.g reports supplement the medical history and physical examination.

In evaluating a patient's cardiac status, two interrelated but separate aspects of heart function are considered individually. These are the myocardial oxygen supply–demand relationship and the function of the heart as a pump. The acquisition and review of the above data allow for the preanaesthetic classification of patients into categories useful in their subsequent care. The New York Heart Association Classification and Goldman's Cardiac Risk Index score are two such schemes (table I). We have found that categorizing the extent of CAD and the state of left ventricular function are more helpful than either of the above schemes or the American Society of Anesthesiologists' Physical Status Classification. We have previously classified these patients into two categories (Waller, Kaplan and Jones, 1979):

(I) Those with signs and symptoms of ischaemic heart disease and good left ventricular function

(II) Those with signs and symptoms of ischaemic heart disease with poor left ventricular function

While such a scheme has proved helpful, we now believe it fails to call attention to another important sub-group, namely those with ischaemic heart disease who have *intermittent* signs and symptoms of left ventricular dysfunction (IA). The majority of patients with symptomatic CAD presenting for elective operations fit into groups I

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TABLE I. *Classification of patients with heart disease. MI = myocardial infarction;* S_3 *= third heart sound; JVD = jugular venous distension; PVC = premature ventricular contraction; BUN = blood urea nitrogen; Creat. = creatinine*

New York Heart Association Classification (Hurst and King, 1978)	Cardiac Risk Index Score (modified after Goodman et al., 1977) Factors	Points
Class 1 = Heart disease, no symptoms	1. History: Age > 70 yr MI < 6 months	5 10
Class 2 = Comfortable at rest, symptoms with ordinary exercise	2. Physical exam: S_3 or JVD	11
	3. E.c.g.: Any rhythm other than sinus > 5 PVC per min	7 7
Class 3 = Comfortable at rest, symptoms with minimal activity Class 4 = Symptoms at rest	4. General information: P_{O_2} < 60 mm Hg P_{CO_2} > 50 mm Hg K$^+$ < 3 mmol litre^{-1} BUN > 50 mg% Creat. > 3 mg% Bedridden	3
	5. Operation: Emergency	4
	Intrathoracic Intra-abdominal Aortic surgery	3
	Total points	50
	Class 1 = 0–5 points 2 = 6–12 points 3 = 13–25 points 4 = 26 points or more	

or IA (table II). The major differences between patients in groups I and II relate to their *response to stress or exercise.* Both groups of patients give historical evidence of good left ventricular function at rest. These patients frequently have angina as their primary problem. They may also have a history of hypertension, but do not have classic findings of chronic left ventricular dysfunction. With exercise, however, patients in group IA become identifiable. Historically, they report the development of dyspnoea, with or without angina, during exercise. Invasive and non-invasive studies of left ventricular function, performed during exercise, often reveal startling impairment of the heart in these patients, whose resting studies are normal or near normal (Bailey et al., 1977; Borer, Bacharach and Green, 1977; Okada et al., 1979). It is little wonder then that resting studies of left ventricular performance often fail to indicate a patient's left ventricular functional response to the stress of exercise or the noxious stimuli of surgery. Patients in group II classically have had one or more myocardial infarctions, and often have signs and symptoms of chronic congestive heart failure and decreased cardiac output. Invasive and non-invasive ventricular function tests may reveal numerous areas of abnormal ventricular wall motion. These patients are likely to have received digitalis, diuretics and even vasodilator drugs before operation to manage their heart failure.

TABLE II. *Classification of patients with coronary artery disease. – = Usually absent; ± = variable; + = usually present.* ETT = exercise tolerance test.

	Group I	Group IA	Group II
Symptoms			
Angina	±	±	±
Dyspnoea:			
At Rest	–	–	+
Exercise	–	+	+
Findings			
Hypertension	±	±	–
E.c.g. change	±	±	±
ETT	±	+	+
LV dysfunction			
At rest	–	–	+
Exercise	–	+	+

Myocardial oxygen balance

The maintenance of the balance between myocardial oxygen supply and myocardial oxygen demand is the *sine qua non* of anaesthetic management for the patient with CAD. The pendulum of emphasis upon either the supply side or the demand side of the oxygen balance equation has swung full cycle during the past decade. Earlier discussions of anaesthetic management of coronary patients stressed the maintenance of oxygen supply,—"avoid hypoxia and hypotension". Subsequent emphasis upon the avoidance of excessive myocardial oxygen demand by controlling heart rate, preload, afterload and contractility gained popularity in the late 70's. The most recent data have refined our understanding of myocardial oxygen demand, and in fact suggest that heart rate and diastolic ventricular volume exert their most important influences on the myocardial oxygen supply side of the balance. This is especially true of the heart rate. A number of investigators have demonstrated that the myocardial oxygen consumption *per beat* remains constant over a wide physiological range of heart rates if preload and afterload are constant (M. B. Laver, 1980, personal communication). Therefore, rapid heart rates exert their primary deleterious effect upon the myocardial oxygen balance by reducing the duration of diastole, and therefore coronary arterial perfusion time. Recently Boudoulas, Rittgers and Lewis (1979) have shown that the relationship between heart rate and the percent of diastole in each cardiac cycle is non-linear. Most perfusion of the coronary arteries distal to significant, partially obstructing lesions occurs after the cessation of electromechanical systole. Therefore, the percent diastole (determined by subtracting the period of electromechanical systole ($Q-S_2$) from the total $R-R$ interval) decreases exponentially with increasing heart rates. Likewise, increased diastolic heart volume (preload) not only increases the myocardial oxygen demand by increasing ventricular wall tension, but also impairs perfusion in the coronary microcirculation since this transmitted tension compresses microscopic intramyocardial and subendocardial vessels. This reduces perfusion (Ellis and Klocke, 1979). In summary, a rapid heart rate and an abnormally high diastolic heart volume are the two aberrations of the determinants of myocardial oxygen supply and demand most likely to produce myocardial ischaemia. Increase in afterload or contractility, the other major indices of oxygen demand, may offset to some degree their own tendency to increase myocardial oxygen demand by simultaneously increasing the arterial pressure and thus the myocardial oxygen supply (Barash and Kopriva, 1980). In the patient with CAD and *good* left ventricular function, hypertension and tachycardia as a result of inadequate attenuation of the responses to noxious stimuli during surgery and anaesthesia are the most likely mechanisms for upsetting the myocardial oxygen balance. Conversely, in patients with ischaemia and *poor* left ventricular function, tachycardia and increased ventricular filling pressure without hypertension are likely to accompany noxious stimulation (Waller, Kaplan and Jones, 1979).

Drug therapy before surgery

The preoperative drug therapy of patients with CAD is based upon all these considerations. It is now generally accepted that patients with CAD should continue their long-term drug therapy until the time of surgery. In fact, many of these same drugs are now administered during operation.

Glyceryl trinitrate (nitroglycerin) has been a mainstay in the management of angina pectoris for more than a century. By its primary effect of increasing venous capacitance and causing peripheral pooling of blood and reduction of venous return, this drug markedly decreases heart size, wall tension and ischaemia (Mason, Zelis and Amsterdam, 1971). Larger doses also produce arteriolar vasodilatation (Hill, Antman and Green, 1981). Nitroglycerin also has been shown to cause a favourable redistribution of coronary blood flow via collateral circulation to subendocardial areas of ischaemia (Mehta and Pepine, 1978).

The beta-adrenergic blocking drugs have been used with increasing frequency in the management of patients with ischaemic heart disease, since they reduce heart rate, arterial pressure and myocardial contractility and also protect against arrhythmias (Ahlquist, 1977). Earlier fears of adverse interactions between beta-adrenergic blocking drugs and anaesthetic agents have proved largely unfounded (with the possible exception of methoxyflurane). Most major cardiovascular centres now recommend the maintenance of patients on beta-blockers until immediately before the surgery, the administration of beta-blockers at the time of premedication, and their further use during operation when anaesthetic drugs fail to control tachycardia (Kaplan and Dunbar, 1976).

Calcium channel blocking drugs represent a relatively new class of drug. They have been used in the treatment of arrhythmia, hypertension, coronary artery disease, and in the protection of the heart from ischaemic damage (Ellrodt, Chew and Singh, 1980). While the exact site of action of these drugs is not established clearly, they appear to block the transit of calcium through the slow channel of the cell membrane and inhibit the release of calcium from various intracellular pools (Henry, 1980). *In vitro* studies have demonstrated dose-related decreases in myocardial contractility which are much greater with some of the calcium antagonists than with others. *In vivo*, however, the primary effect of most of these drugs is a decrease in vascular resistance which occurs in the coronary, systemic, and pulmonary vascular beds (Zsoter, 1980). Nifedipine, a prototype of this class of drug, has produced its most striking results in the treatment of variant angina (Antman et al., 1980). This can be explained by its ability to prevent coronary vasospasm. While it is also effective in the management of classical angina, it has not been proven to be superior to the standard treatment with beta-blocking drugs and nitrates in prevention of anginal attacks. However, it may be a useful additional drug in patients with this condition.

E.C.G. MONITORING

E.c.g. monitoring for detection of myocardial ischaemia is now standard practice in the operating room. Earlier studies of e.c.g. monitoring during operation referred primarily to standard limb lead II (Cannard, Dripps and Helwig, 1960). Lead II was chosen because its axis parallels the P-wave vector, thus making identification of the P-wave easier and aiding in the differentiation of supraventricular from ventricular arrhythmias. Although cardiologists have long recognized that precordial leads are the most likely to detect ST-segment changes during conventional exercise electrocardiography (Mason, Likar and Biern, 1967), it was not until the 70's that this information was widely applied to the operating room setting. Foëx and Prys-Roberts (1974), Dalton (1976) and Kaplan and King (1976) recommended various systems which include a precordial lead for the detection of ischaemia during operation in patients with CAD. A system allowing the simultaneous observation of a precordial lead (V_5 or CM_5) and lead II, using two separate e.c.g. channels, permits the detection of both anterior and inferior myocardial ischaemia. ST–T wave changes seen in a precordial lead usually correspond to ischaemia of the left ventricle. With the e.c.g. standardized to 1 mV per 10 mm, a 1-mm horizontal or down-sloping ST segment depression from baseline represents significant myocardial ischaemia, and greater magnitudes of depression are generally thought to represent increased ischaemia. Up-sloping ST segment depression (J-point depression) and various T-wave changes may reflect ischaemia, but are not specifically diagnostic. ST segment elevations of greater than 1 mm usually represent transmural myocardial ischaemia (Belic and Gardin, 1980).

In several centres there has been a recent renewal of interest in e.c.g. tracings obtained from endocardial or oesophageal electrodes (Kistin and Bruce, 1957). Positioning of these electrodes to maximize P-wave amplitude can greatly simplify the diagnosis of supraventricular arrhythmias (fig. 1). It is not yet clear if important information regarding subendocardial ischaemia can also be obtained from these electrodes.

Various invasive and non-invasive monitoring devices have been used to detect the changes in global or regional myocardial performance which are often associated with myocardial ischaemia. Sudden reductions in ejection fraction, new ventricular wall motion abnormalities and the sudden onset of papillary muscle dysfunction have been detected by echocardiography (Elliot et al., 1980) or real-time radionuclear techniques (Barash et al., 1980) during anaesthesia. Additionally, increases in the amplitude of the A or V waves, or both, in a pulmonary capillary wedge pressure tracing have been observed to occur with, or even precede, the development of ST segment depression on the e.c.g. during stimulation in these patients (Wells and Kaplan, 1980) (fig. 2).

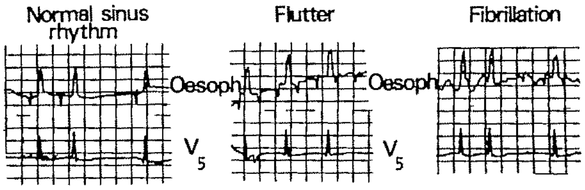

FIG. 1. Progression of arrhythmia. An oesophageal e.c.g. tracing (oesoph) is compared with a precordial (V_5) tracing. The ease of P-wave identification facilitates diagnosis of the progression from normal sinus rhythm (left) to atrial flutter and fibrillation (centre and right) which is not clearly shown by the surface e.c.g.

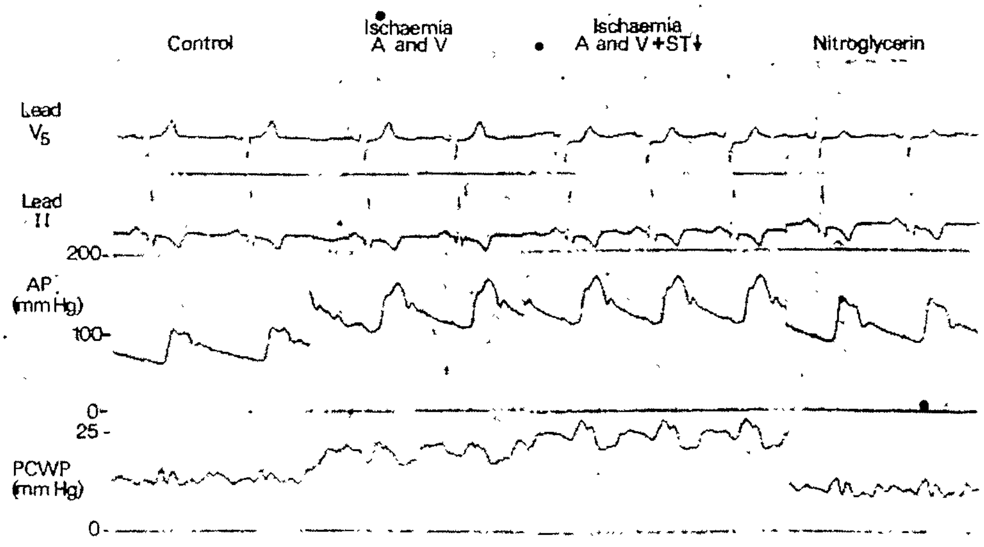

FIG. 2. The development and reversal of ischaemia accompanying the response to tracheal intubation. Note that the development of large A and V waves (Ischaemia A and V) in the wedge tracing, compared with the control tracings, heralds subsequent development of ST segment depression (A and V + ST↓). Treatment with nitroglycerin i.v. first returned the wedge tracing to normal, and then reversed the ST segment depression in lead V_5.

Although the meaning of such changes has not been elucidated fully, they may be an indication of the reduction in diastolic ventricular compliance, which appears to represent the earliest detectable change of myocardial ischaemia in the cardiac catheterization laboratory (Wiener, Dwyer and Cox, 1968). Therefore, whilst e.c.g. monitoring remains the standard method of detecting ischaemic changes, various monitors which can detect early changes in regional ventricular performance may yield earlier and more precise information regarding the development and progression or regression of ischaemia (Barnard, Buckberg and Duncan, 1980).

ANAESTHESIA

The major goals of intraoperative care in patients with CAD are to prevent or treat myocardial ischaemia while preserving or improving left ventricular function. The methods of achieving these goals are fundamentally different in patients with good left ventricular function as opposed to those with very poor left ventricular function. In general, the major focus of therapy in patients with good ventricular function is to produce an anaesthetic state sufficiently deep to assure attenuation of the autonomic responses to noxious stimuli while still preserving adequate haemodynamic function. No one technique using single or multiple anaesthetic drugs, with or without the addition of vasoactive agents, has been shown to be superior to any other technique. Therefore, the approach to these patients varies widely among major cardiovascular centres. In patients with good left ventricular function, ischaemia is often the result of a hyperdynamic circulatory state in which heart rate, arterial pressure and, at times, ventricular filling pressures are increased. Therefore, the use of anaesthetic drugs which produce controllable myocardial depression has become increasingly popular. The short-acting thiobarbiturates, such as thiopentone, enjoy wide use for the induction of anaesthesia in this group of patients. The barbiturates depress myocardial contractility, reduce ventricular filling pressures secondary to venous pooling of blood, and reduce the sympathetic nervous system outflow, tending to decrease myocardial oxygen demand (Seltzer, Gerson and Allen, 1980).

Large doses of the narcotic analgesics have also been recommended by Lowenstein and others (1969) as induction agents for patients with CAD. The failure of even very large doses of morphine to provide adequate amnesia and reflex attenuation in patients with good left ventricular function has been known for some time (Lowenstein, 1971). Recently, the suggestion has been made (Lunn et al., 1979) that use of large doses of fentanyl without the addition of the other anaesthetic drugs overcomes these problems. However, Waller and others (1981) have shown that this technique may also fail to provide adequate reflex blockade. Despite the limitations of narcotic anaesthetics as sole induction agents for these patients, they clearly have a role in augmenting other anaesthetic measures. The combination of narcotics with benzodiazepines or butyrophenones has also been recommended (Stanley, Bennett and Loeser, 1976). Diazepam is one of the benzodiazepines widely used for this purpose (Jones, Stehling and Zauder, 1979). It has become popular because of the profound amnesia produced and its relatively benign effects on the cardiovascular system, including a slight reduction in arterial pressure and little change in cardiac output and filling pressures (McCammon, Hilgenberg and Stoelting, 1980). In addition, a coronary vasodilator effect of diazepam has been suggested (Ikram, Ruben and Jewkes, 1973), and there is evidence that, in patients with increased left ventricular filling pressures, a small dose of diazepam can reduce this pressure (Côté, Campeau and Bourassa, 1976).

After the patient loses consciousness, inhalation drugs are commonly used as a part of the technique in the United States. Fifty percent nitrous oxide in oxygen, plus potent volatile agents such as enflurane, halothane or isoflurane may be administered to obtain an adequate depth of anaesthesia before the stimulus of tracheal intubation. The combined effect of these drugs produces some depression of left ventricular performance, which aids in preventing undesirable increases in arterial pressure and heart rate during laryngoscopy and intubation (Roy, Edelist and Gilbert, 1979). The potent volatile anaesthetics are especially useful during operation since they provide controllable, rapidly reversible, myocardial depression. Halothane has been shown to reduce myocardial work and oxygen consumption (Sonntag et al., 1979), and may increase the coronary vascular reserve (Merin, 1980; Verrier et al., 1980). Bland and Lowenstein (1976) showed that 1-MAC halothane anaesthesia reduced the severity of myocardial ischaemia caused by coronary ligation in dogs. Enflurane and isoflurane also cause dose-dependent myocardial depression and they appear to produce more arteriolar dilatation and fewer arrhythmias than does halothane (Delaney et al., 1980).

The narcotic analgesics are used most often for anaesthetizing patients with poor left ventricular function, since they are relatively free of myocardial depressant properties. Morphine continues to be used widely in doses ranging from 0.5 to 3 mg kg^{-1} body weight. Recently, attention has been focused upon the substitution of large doses of fentanyl for morphine in narcotic anaesthetic techniques. Fentanyl appears to be desirable because it evokes little if any histamine release and therefore is less likely than morphine to produce hypotension during induction of anaesthesia. Doses ranging from 50 to 150 µg kg^{-1} have been shown to produce cardiovascular stability and attenuation of sympathetic responses to noxious stimulation (Lunn et al., 1979). Preliminary work with sufentanil and other fentanyl analogues suggests that they may be superior to fentanyl in this regard (de Lange, Stanley and Boscoe, 1980). Nitrous oxide, which has relatively benign haemodynamic effects in patients with good ventricular function, may not be tolerated by the sickest patients because of its myocardial depressant properties. However, it is often helpful when used intermittently during the most stressful periods of an operative procedure. The potent volatile anaesthetics usually are not used in this group of patients because of their myocardial depressant effects.

The preceding discussion has focused on the anaesthetic management of patients with either good or poor left ventricular function. However, there is a spectrum of left ventricular function apparent during surgery. Patients starting with good left ventricular function may demonstrate signs of myocardial dysfunction during periods of stress or ischaemia. Conversely, patients with impaired left ventricular function may show improvement with decreased oxygen consumption under anaesthesia. Therefore, the majority of patients should be considered to be in a dynamic state, with ventricular function varying throughout the course of anaesthesia and surgery. For this reason, the choice of anaesthetic and cardioactive drugs should be made and constantly reassessed for each individual patient, based upon information derived from continuous monitoring. We have found that the induction of anaesthesia with a narcotic and tranquillizer combination is useful even in patients with good left ventricular function (Waller, Kaplan and Jones, 1979). Using this basal anaesthetic, low concentrations of the potent inhalation anaesthetic agents can be added as needed to achieve adequate depth of anaesthesia. Thereafter, should the patient's ventricular function deteriorate, the volatile agent can be eliminated quickly.

PHARMACOLOGICAL INTERVENTION

Despite the most skillful manipulation of anaesthesia, ischaemia still may result during surgery. Recognition of this fact has led to the use of a variety of drugs to treat ischaemia and to prevent it. Vasodilators and beta-adrenergic receptor blocking drugs are the primary agents used for this purpose (table III). Vasodilators are used to treat episodes of hypertension, increased left ventricular filling pressure or coronary artery spasms. I.v. nitroglycerin (Kaplan, Dunbar and Jones, 1976) and sodium nitroprusside (Lappas, Lowenstein and Waller, 1976) are the drugs most commonly used. Other vasodilators, such as phenothiazines, ganglionic blocking drugs, and alpha-adrenergic receptor antagonists are sometimes used. These drugs produce varying degrees of arteriolar and venous dilatation with variable effects on preload, afterload and overall haemodynamics. Nitroglycerin is our drug of choice during operation for patients with CAD in the following situations: hypertension; increased pulmonary capillary wedge pressure or the appearance of large A and V waves in the wedge pressure tracing; e.c.g. changes of ischaemia; coronary artery spasm; recent or evolving myocardial infarction.

In selected situations, nitroglycerin and phenylephrine may be used in combination. Borer, Redwood and Levitt (1975) have shown that this combination may reduce myocardial ischaemia more than nitroglycerin alone. The rationale is that nitroglycerin decreases the preload of the heart while the vasopressor maintains diastolic perfusion pressure during the administration of the vasodilator. We have found this drug combination to be especially useful in patients with either severe left main coronary artery disease or unstable angina.

Patients with poor left ventricular function may require inotropic support during the course of an anaesthetic. Calcium chloride and ephedrine are useful when administered in bolus forms, since they are relatively short-acting and produce moderate increases in myocardial contractility (Hug and Kaplan, 1979). More intense and prolonged inotropic support may be provided by the infusion of sympathomimetic drugs such as dobutamine, dopamine or, in the most extreme situations, adrenaline, noradrenaline or isoprenaline. Many investigators have shown that vasodilators such as nitroprusside may be added to the inotropic drugs to maximize their effects on cardiac output and ventricular function.

TABLE III. *Therapeutic interventions for ischaemia*

Associated with:	Treatment
Increased arterial pressure	a. Deepen anaesthesia b. Vasodilator c. Beta-blocker
Increased heart rate	a. Deepen anaesthesia b. Beta-blocker
Increased PCWP or CVP	a. Vasodilator b. Restrict fluids c. Diuretic d. Inotropic agent
Decreased arterial pressure	a. Lighten anaesthesia b. Restrict fluids c. Inotropic agent or vasopressor
Arrhythmias	a. Lignocaine b. Beta-blocker c. Calcium-blocker
Coronary artery spasm	a. Vasodilator b. Calcium-blocker

SUMMARY

Safe anaesthetic management techniques for patients with coronary artery disease have been devised. Thorough familiarity with the underlying pathophysiological principles, and the techniques for circulatory monitoring and anaesthetic management is required if optimal anaesthetic care is to be assured.

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CARDIOVASCULAR MONITORING IN PATIENTS WITH VASCULAR DISEASE

C. PRYS-ROBERTS

The monitoring of vital functions during anaesthesia in any patient is dependent on the predictability of that patient's responses to drugs, ventilation techniques, and other manoeuvres associated with anaesthesia, as much as on the responses to the varieties of surgical injury. When the course of events is highly predictable, cardiovascular monitoring can be limited to the continuous or intermittent non-invasive measurement of certain variables: the electrocardiogram with heart rate derived and arterial pressure by an intermittent sphygmomanometric technique. Surveillance of the patient with hypertension or atheromatous vascular disease, or both, during anaesthesia and surgery requires a more rigorous approach than for the normal healthy patient. This is necessary because of the unpredictable behaviour of these patients in response to almost every aspect of anaesthesia and surgery. As perioperative morbidity and mortality are increased in this group of patients (Arkins, Smessaert and Hicks, 1964; Chamberlain and Edmonds-Seal, 1964; Foëx and Prys-Roberts, 1974; Steen, Tinker and Tarhan, 1978; Goldman and Caldera, 1979; Eerola et al., 1980) and can often be related to episodes of cardiovascular dysfunction during and after anaesthesia, the application of many invasive monitoring techniques can be more readily justified.

The key to the predictability of cardiovascular response to anaesthesia and surgery lies, perhaps surprisingly, more in the pathophysiological state of the systemic arterial system than in the heart. Patients with occlusive atheromatous disease of the coronary arteries, however severe, show relatively predictable responses to the noxious stimuli of surgery. By contrast, patients with essential hypertension, whether adequately treated or not, show markedly exaggerated pressor and heart rate responses to noxious stimuli such as laryngoscopy, surgical incision or mesenteric traction (Prys-Roberts et al., 1971; Prys-Roberts, 1980a). Patients with hypertension of renovascular origin show less exaggerated pressor responses than those with essential hypertension only because their baseline arterial pressures, both systolic and diastolic, are consistently higher (Prys-Roberts, 1979). One group of patients who show even more exaggerated responses are those with rigid arteriopathy as a result of arteriosclerosis (Prys-Roberts, 1980a); they may be recognized by their characteristic arterial pressure variability on a day-to-day basis. At rest, their arterial pressures are characterized by a systolic pressure variation between 150 and 180 mm Hg, but a consistent diastolic pressure less than 90 mm Hg. Exercise, emotional stress or apprehension are associated with a marked increase of systolic arterial pressure to considerably more than 200 mm Hg with little change of diastolic arterial pressure. These patients have a greater than normal resting systemic vascular resistance, but their systolic arterial pressure changes are almost entirely secondary to changes of stroke volume. Consequently, the depressant effects of anaesthetics or the onset of junctional arrhythmia may cause dramatic decreases of systolic arterial pressure, while noxious stimuli cause equally dramatic increases.

The purpose of this paper is to define the pathophysiological dysfunctions which occur in arteriopathic patients, and to explore the justification of various aspects of cardiovascular monitoring in these patients.

CORONARY ARTERY DISEASE

Monitoring of the patient with coronary arterial disease is predominantly dedicated to identifying the onset of myocardial ischaemia and its pathophysiological consequences with the objectives of reversing the causative factors or protecting the ischaemic myocardium. Atheromatous coronary artery disease is common in patients with high arterial pressure, accounting for the death of about

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60% of all patients with hypertension. Myocardial ischaemia, as a manifestation of coronary artery disease, is a common finding during anaesthesia in patients with hypertension, especially those who have not received beta-receptor antagonists (Prys-Roberts and Meloche, 1980).

ELECTROCARDIOGRAPHY

Inadequate perfusion of any tissue leads to alterations in the surface charges on the cells as a result of the hypoxic failure of the Na^+–K^+ pump which is dependent on ATP. The cumulative effect of such an injury current modifies the action potentials of a mass of cardiac muscle cells with consequent changes in the surface electrocardiogram. The final alteration of the ST segment of the surface electrocardiogram will depend on the regional distribution of ischaemia and also on the siting of the electrodes used for its detection. Two types of ischaemic pattern can be recognized clinically: ST segment elevation characteristic of transmural ventricular wall ischaemia (fig.1) and ST segment depression characteristic of subendocardial ischaemia (Kupersmith, 1977). The severity of coronary artery disease can be predicted from the relationship between ST segment depression and the heart rate (Elamin et al., 1980).

ST segment elevation is typical of the gross transmural ischaemia which occurs as a result of total occlusion of a major coronary artery and is a prelude to transmural myocardial infarction. ST segment elevation may also occur in Prinzmetal's variant angina (Prinzmetal, Kennamer and Kwoczynski, 1960), which is believed to be caused by spasm of major coronary arteries to such an extent as to cause transmural ischaemia. Prinzmetal's angina may occur during or after anaesthesia (Balagot et al., 1977; Krantz, Viljoen and Gilbert, 1980) and should be considered as a differential diagnosis of acute myocardial infarction. The diagnosis is important as beta-receptor antagonists are contraindicated and coronary vasodilators such as glyceryl trinitrate or calcium antagonists such as nifedipine are specifically indicated.

Subendocardial ischaemia

Although Salisbury, Cross and Rieben (1963) recognized that the inner layer of the ventricular myocardium could become selectively ischaemic, the concept of subendocardial ischaemia as the common manifestation of inadequate coronary arterial perfusion has been recognized widely only during the past 8 years. The anatomical layout of myocardial wall perfusion is such that penetrating branches of the main epicardial coronary arteries perfuse the subepicardial and middle cardiac layers without a significant collateral circulation. The subendocardium is at the distal end of this perfusion pathway, and in normal man there is minimal collateral perfusion. Unlike all other circulatory segments, the coronary system is predominantly (95%) perfused during diastole, and the flow in these penetrating arteries is determined by the pressure gradient between the main epicardial arteries (aortic diastolic pressure) and the subendocardium (left ventricular diastolic pressure), and by the duration of diastole. In the

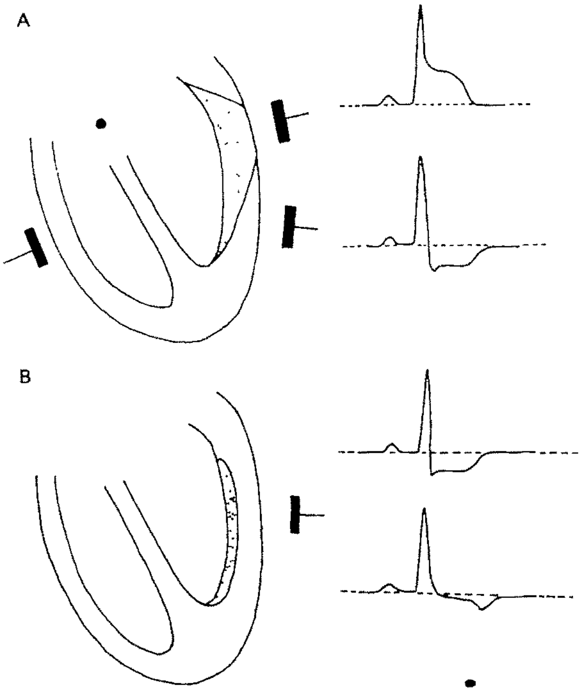

FIG. 1. Electrocardiographic appearances of transmural myocardial ischaemia (above) and subendocardial ischaemia (below). A wedge-shaped area of ischaemia secondary to complete occlusion or spasm (Prinzmetal's angina) of a major epicardial artery may produce the characteristic elevated ST segment in a chest lead which overlies the ischaemic segment, or ST segment depression in an adjacent lead overlying a marginal area of subendocardial ischaemia. Generalized subendocardial ischaemia is associated with ST segment depression (upper trace) and may progress to infarction in which T wave inversions occur (lower trace).

patient with established coronary artery disease, the subendocardial collateral circulation may be crucial to adequate perfusion of some areas of the myocardium (Guy and Elliott, 1970; Holsinger and Elliott, 1972), especially when the transmyocardial perfusion pressure is decreased. This may occur when aortic diastolic pressure is decreased or if the left ventricular diastolic pressure increases simultaneously with the onset of transient left ventricular failure. Such episodes have been described following laryngoscopy (Prys-Roberts et al., 1971), cross-clamping of the aorta (Attia et al., 1976), splitting of the sternum (Kaplan, 1980) and during the period of recovery from surgery.

Lead selection

Detection of ST segment changes occurring in the distribution of the left coronary artery and its branches supplying the left ventricular myocardium requires a lead placement which can be predicted to maximize the display of the voltage change. Blackburn and colleagues (1967) studied all the available lead placements and concluded that the unipolar chest leads V4 and V5, and especially the bipolar lead CM5 gave better than 80% detection of ST segment changes, whereas the standard limb leads I, II and III gave less than 30% detection. The application of the V5 and CM5 lead placement has been recommended for use during anaesthesia and surgery in patients with a potential for developing myocardial ischaemia (Prys-Roberts et al., 1973; Kaplan and King, 1976; Prys-Roberts, 1980b).

Detection of arrhythmia is not impaired by the use of these specific leads and is an important aspect of the management of the patient with coronary artery disease. Perhaps the most disruptive arrhythmia in these patients, especially those with hypertension, is junctional rhythm at a slow rate (< 50 per min) (see later section on pulmonary artery pressures).

MEASUREMENT OF INTRAVASCULAR PRESSURES

Arterial pressure

The arterial pressure wave contains a wealth of information about many aspects of cardiovascular function, available on a beat-by-beat basis. However, most clinicians are accustomed to derive only three variables from the arterial pulse—the systolic and diastolic pressures, and the heart rate. These, of course, yield more than adequate information in the normal patient when recorded intermittently, either by the standard Riva-Rocci technique or with the oscillotonometer. The accuracy of the former has often been called in question (Geddes, 1970), but it is surprising that no comprehensive study of the oscillotonometer has ever been made since its introduction in the late twenties.

For non-invasive intermittent measurements in the patient with ischaemic heart disease or hypertension, various automatic or semi-automatic systems are available based on ultrasonic pulse detectors (Roche Arteriosonde 1225, Kontron Medical) or the oscillotonometer principle (Dinamap 845, Applied Medical Research).

For major surgery in patients with cardiovascular disease, the monitoring of arterial pressure by direct cannulation of a peripheral artery should be regarded as routine. Enough has been written in numerous texts on the techniques of arterial pressure measurement, and the emphasis in this paper will be on some new and specific applications and advantages of arterial pressure monitoring. Given that the arterial pressure wave has been faithfully recorded, certain features of the waveform are useful in assessing the state of the circulation (fig. 2).

Arterial d*P*/d*t* (*rate of change of pressure*)

The sudden increase of arterial pressure at the onset of systole reflects the changes of pressure which occurred during the period of isometric left ventricular contraction, and thus can give an indication of the contractile state of the myocardium. Aortic d*P*/d*t* is closely correlated with left ventricular d*P*/d*t* (Taylor, Snow and Linden, 1972). In practice, it is not necessary to use a differentiator to give an accurate value of arterial d*P*/d*t* (Gersh, Hahn and Prys-Roberts, 1971), as it is quite simple to visualize on an oscilloscope screen whether or not the rate of change of pressure is rapid, indicating good contractile performance, or sluggish, indicating poor contractility.

Stroke volume

The area under the systolic ejection part of the aortic pressure curve (fig. 2) is related to stroke volume by a relationship which has been variously characterized during the past 50 years (Nichols, 1973; McDonald, 1974). The uniform transmis-

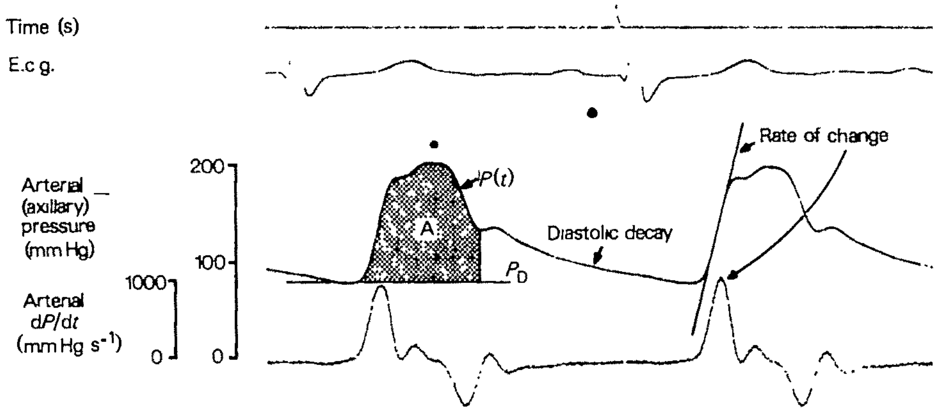

FIG. 2. A typical arterial pressure waveform (axillary or brachial) showing three sections from which useful information can be derived. The leftmost pressure wave shows the derivation of stroke volume from the area under the systolic ejection curve (between the onset of the pulse and closure of the aortic valve). The rightmost pressure curve shows the derivation of the rate of change of arterial pressure (arterial dP/dt) as the maximum slope of the upstroke of the arterial pressure. The pressure signal can be electronically differentiated to produce the dP/dt signal shown beneath. The diastolic downslope of the arterial pressure wave can be processed mathematically as an exponential decay to yield information about the resistance and capacitance of the arterial system.

sion line model yields a mathematical relationship (Wesseling et al., 1976) in which stroke volume (SV) is given by:

$$\mathrm{SV} = \frac{1}{Zo} \int_{P_D}^{P(t)} [P(t) - P_D]\,dt$$

where Zo is the characteristic impedance of the systemic arterial system; $P(t)$ = instantaneous pressure at time t; P_D = diastolic pressure; $\int_{P_D}^{P(t)} [P(t) - P_D]\ dt$ = area under the systolic pressure $P(t)$ curve.

This formula has been used as the basis of an analog computing system which derives the cardiac output, stroke volume, heart rate and other variables from an input signal derived from the aortic pressure (Wesseling et al., 1976). A more recent development in the author's department, based on the same equation, utilizes a microprocessor-based microcomputer to produce a beat-by-beat estimate of the stroke volume (fig. 3). The latter system can be programmed to correct the computed stroke volume for changes in systemic vascular resistance. Although derivations of stroke volume can also be made from the axillary or brachial arterial pulse, the radial artery pulse is too distorted by reflected waves to give a true estimate of stroke volume.

Systemic vascular resistance

The characteristics of the diastolic downslope of the arterial pressure wave are determined largely by the leakage of the ejected stroke volume into the systemic vascular bed which, having compliance (capacitance) and resistance, allows the pressure to decay usually as a simple exponential. Drugs and physiological events which alter systemic vascular resistance, by causing either peripheral arteriolar constriction or dilatation, cause marked changes in the shape of the diastolic pressure decay. Decreased arterial pressure associated with arteriolar dilatation can be identified by the characteristic loss of the diastolic pressure decay after the dicrotic notch. This is typical of changes during hypotension induced with sodium nitroprusside, but may occur in patients with arteriovenous fistulae, or in patients with severe anaemia. Increased arterial pressure with a high dicrotic notch (indicating early limitation of ejection) and a steep diastolic pressure run-off is characteristic of increased vascular resistance in response to vasoconstrictor drugs such as phenylephrine, or naturally induced changes in the severe hypertensive patient.

In the patient with hypertension in particular, in whom the pressure changes may be dramatic, direct recording of arterial pressure is frequently essential in order to alert the anaesthetist of beat-by-beat changes of arterial pressure which require his attention.

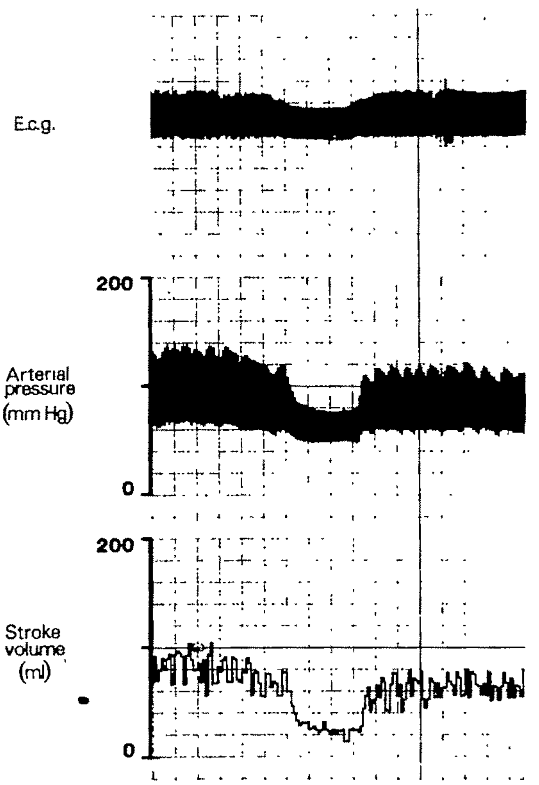

FIG. 3. Output of the microprocessor-based system to yield beat-to-beat stroke volume estimates (J. H. Curnow and C. Prys-Roberts, unpublished data) during an induced Valsalva manoeuvre. The variability of stroke volume with ventilation before and after the manoeuvre, and the decrease of stroke volume during the manoeuvre, are clearly shown.

Central venous pressure

The main objective in measuring central venous pressure (CVP) is to estimate right ventricular end-diastolic pressure and thus to obtain an indication of the filling characteristics of the ventricles. At this point it is worth emphasizing that the two variables of the Frank–Starling Law are energy of contraction and resting fibre length. Ventricular end-diastolic volume is a first order approximation to the change of length of various myocardial fibres, and end-diastolic pressure is not linearly related to volume (see later section on left ventricular pressures). Thus central venous pressure, whether measured by a saline manometer or by an electronic transducer, is only an approximation to the true filling characteristic. Nevertheless, used sensibly, it can provide useful information.

A single value of CVP is of little use in estimating the state of the circulation, or of the blood volume. A CVP of 3 mm Hg may represent a hypovolaemic patient with mild congestive cardiac failure, a hypervolaemic but venodilated anaemic patient, a patient after a recent haemodialysis with hypovolaemia masked by venoconstriction, or a normal resting patient. The response of each of these patients either to induction of anaesthesia or to volume loading, would be very different. To obtain the best information from measurements of CVP, one should rapidly infuse saline 250 ml in the conscious patient before anaesthesia, and observe the rate of increase of CVP, the peak value, and the time taken for the CVP to return to the baseline value. This procedure should ideally be repeated during established anaesthesia before the onset of surgery in order to characterize fully the patient's response to volume loading. Volume loading the anaesthetized hypertensive patient usually causes a modest increase of CVP (from 3 to 6 mm Hg), whereas the PA wedge pressure increases by a comparable amount (6 mm Hg) from a greater resting value of 10 mm Hg (Prys-Roberts and Meloche, 1980). A patient with incipient heart failure could be expected to increase CVP from a resting value of 8 mm Hg to about 15 mm Hg.

Pulmonary arterial pressures

The development of the balloon-tipped flow-guided pulmonary artery catheter (Swan et al., 1970) revolutionized the indirect measurement of left atrial pressure, and has contributed greatly to the improved care of the patient with left ventricular dysfunction whatever its cause. In normal man, left atrial pressure is about 4–5 mm Hg greater than right atrial pressure, the difference reflecting the lower diastolic compliance of the thicker walled left ventricle. In a recent study of patients with coronary artery disease, Mangano (1980) found that, in patients with ejection fractions greater than 50% and with no angiographic evidence of left ventricular dyssynergy, absolute values and changes of pulmonary arterial wedge pressure (PAWP) correlated well with those of CVP. By contrast, in patients with ejection fractions of less than 40% or with dyssynergy, there was no correlation between PAWP and CVP. He thus provided some evidence that, in the patient with ischaemic heart disease and good cardiac function, CVP was an adequate estimate of ventricular filling pressure. Interpretation of Mangano's data is a little difficult, however, because the perturbations of both left and right filling pressures were brought about by deliberate changes of body posture, and not by alterations of afterload.

Figure 4 shows ventricular function curves relating left ventricular stroke work index (LVSWI) and left ventricular end-diastolic pressure (LVEDP), and a collateral relationship between left ventricular end-diastolic volume (LVEDV) and LVEDP. Data from normal subjects (Ross and Braunwald, 1964; Parker and Case, 1971) show that values obtained at normal heart rates and fluid loading conditions lie at the shoulder of the curve, indicating a very limited reserve of the Starling mechanism. Below this point, quite large reductions of blood volume can decrease LVEDV by more than 50% and yet LVEDP may decrease by only 2–3 mm Hg. By contrast, above this shoulder, very small increases of LVEDV cause large increases of LVEDP, but are associated with negligible improvement of cardiac performance. The same of course is true of the similar relationships in the right ventricle, although the same volume changes are associated with lower pressures (reflected in CVP) because of the greater compliance of the thinner right ventricular wall.

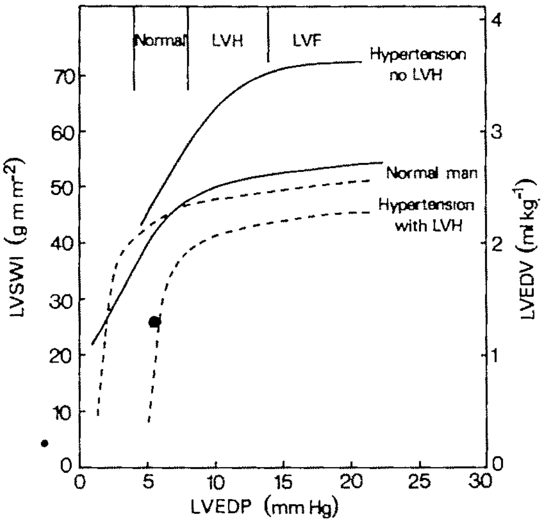

FIG. 4. Left ventricular function and compliance curves for normal and hypertensive patients. The data for the normal curves were derived from Parker and Case (1971) and Ross and Braunwald (1964). The continuous and interrupted lines (normal man) indicate the LVSWI/LVEDP: ventricular function curve, and LVEDV/LVEDP: ventricular compliance curves respectively. The bands (upper left) indicate the range of LVEDP found in normal man, and in hypertensive patients with either uncomplicated LV hypertrophy (LVH) or LV failure (LVF). The hypertensive patient without evidence of LVH may have a ventricular function curve well above that of normal man, whereas the patient with LVH shows a compliance curve (interrupted line) shifted well to the right of normal. The latter curve is an "idealized" construction to demonstrate the influence of LVH.

The patient with hypertension of long duration, or with severe hypertension, develops left ventricular hypertrophy as an adaptive phenomenon in the face of persistently increased aortic impedance (Folkow, 1978), the main component of left ventricular afterload. The thickened walls of the hypertrophic left ventricle have a low diastolic compliance and consequently the LVEDP is greater by between 5 and 15 mm Hg than in the normal patient. The patient whose hypertension is mild (diastolic pressure < 110 mm Hg) or well controlled with with antihypertensive drugs will probably have compliance and function curves within the normal range, so that CVP measurements can be regarded as potentially accurate reflections of LVEDP. Patients whose hypertension is severe despite antihypertensive therapy, or untreated (diastolic pressure > 120 mm Hg), usually have symptoms or signs, or both, of left ventricular hypertrophy (LVH). Figure 4 depicts the resting ventricular function curve for hypertensive patients without LVH and an "idealized" compliance curve for patients with LVH. In these latter patients normal LVEDV and stroke volumes can only be achieved at values of LVEDP well above normal. In these patients CVP is within the normal range.

Of the many influences which may decrease ventricular filling, haemorrhage or the onset of junctional rhythm (fig. 5) cause severe perturbation of arterial pressure in patients with LVH. Junctional rhythm is easily recognized by standard e.c.g. monitoring techniques, and in patients with normal hearts causes only minor perturbations of arterial pressure. In the patient with LVH, the loss of the atrial contribution to ventricular filling can have a catastrophic effect (fig. 5) on a left ventricle accustomed to a high end-diastolic pressure. Resolution of filling restores ventricular diastolic distension and systolic ejection improves dramatically. Thus, in the patient with LVH, a Swan–Ganz catheter can give essential information, especially in those patients undergoing surgery in which conflicting perturbations are likely to occur, for instance aortic grafting for aneurysm

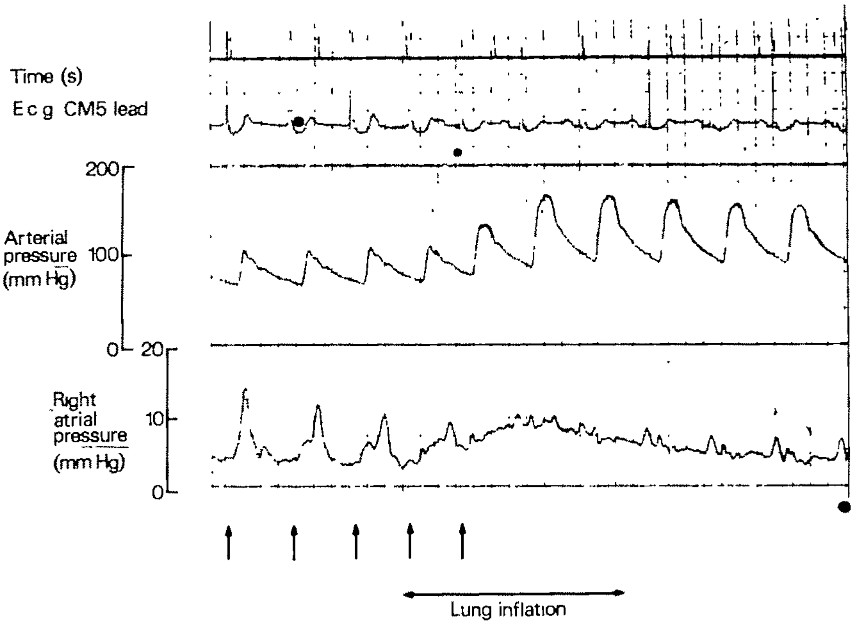

FIG. 5. Cyclical change from junctional rhythm (arrowed beats) to sinus rhythm in a patient with LV hypertrophy secondary to hypertension. The arterial pressure waves (arrowed) show a rapid rate of rise, indicating adequate contractile performance, but a shortened triangular ejection phase characteristic of inadequate ventricular filling. The normal beats show that the dP/dt is similar to the arrowed beats, but the ejection phase is increased and the rounded pressure wave is characteristic of adequate ventricular filling. The Cannon waves in the R atrial pressure trace are characteristic of junctional rhythm.

or occlusive disease. The combinations of anaesthetic effects, surgical manipulation of mesentery, haemorrhage, cross-clamping of the aorta and the acute hypotension which may accompany unclamping of the grafted arteries, may cause episodes of arterial hypotension or hypertension which are difficult to interpret without a knowledge of left ventricular filling pressures. Acute hypertension occurring during the recovery period immediately after operation may induce acute left ventricular failure with pulmonary oedema. Continuous monitoring of the PA diastolic pressure with intermittent checking of the PCWP can alert recovery room staff and the anaesthetist to the onset of this complication.

NON-INVASIVE CARDIAC MEASUREMENTS

Measurement techniques which do not "invade" the patient's skin or do not cause pain or injury to tissues are consistently popular with clinicians who, quite justifiably, wish to cause as little discomfort as possible to their patients. Most non-invasive techniques related to the cardiovascular system do not directly measure a physical quantity which is relevant to physiological performance, but rely on a strong statistical correlation between the non-invasive and a directly measured variable. Two good examples of such correlation are:

Rate–pressure product (*RPP*). The product of heart rate and systolic arterial pressure correlates strongly with directly estimated myocardial oxygen uptake (Nelson et al., 1974). While this index is useful as a guide to increased myocardial oxygen uptake during anaesthesia in patients with hypertension and coronary artery disease (Roy, Edelist and Gilbert, 1979; Prys-Roberts, 1980b), it may be of less value as a predictor of myocardial oxygen uptake when the values are reduced to less than normal (Sonntag et al., 1979) as may occur during stable halothane anaesthesia. The RPP is a useful index of the angina threshold in anaesthetized patients who may develop myocardial ischaemia during surgery. Reves and colleagues (1979) found that, whereas the mean values of RPP in response to noxious stimuli during anaesthesia did not exceed the anginal threshold RPP of the same patients before operation, in two patients out of 19 the angina threshold was exceeded during surgery.

Pre-ejection period (PEP) is one of the systolic time intervals which has received considerable attention over the past 15 years, especially by anaesthetists. PEP was originally introduced and studied as an index which could identify depressed left ventricular performance in patients with mild to severe heart failure (Weissler, Harris and Schoenfeld, 1969). More recently it was suggested that PEP was an index of myocardial contractility (Reitan et al., 1972) and as such it became popular as an investigative index, despite the fact that it has been well documented that PEP is highly dependent on changes of heart rate, preload (CVP or PCWP) and afterload (aortic impedance) (Talley, Meyer and McNay, 1971), and is a poor correlate of some inotropic changes in normal man (Weissler, Gamel and Grode, 1964). A further drawback to the index is that three separate measurements—e.c.g., a recording of the carotid pulse and a phonocardiogram—are required in order that the pre-ejection period may be derived as the difference between the total electromechanical time (Q wave of e.c.g. to S_2 (second heart sound)) and the left ventricular ejection time (LVET). As a general principle, the derivation of a small number, as the difference between two relatively large numbers, is fraught with the possibility of large errors (Smith, 1980). It has been proposed that the normalization of PEP by the LVET reduces some of the problems outlined above. However, that normalized index, PEP/LVET, has no physical dimensions (time divided by time)—a difficult feature to reconcile with the estimation of myocardial performance!

Derivation of stroke volume from the thoracic impedance cardiogram

If an electrode system affixed to the skin around the neck and around the lower thorax is excited by a 100-kHz sinusoidal current of about 4 mA, the electrical impedance across the thoracic cage changes in a pulsatile manner and the characteristic waveform can be processed to yield values of stroke volume (Kubicek et al., 1966).

Four disposable mylar strip electrodes (fig. 6) affixed around the neck and lower thorax are connected in a four-terminal system. If a constant current (4 mA r.m.s. at 100 kHz) is applied across the electrodes, changes of transthoracic impedance are reflected as changes of potential between the electrodes (fig. 6). Kubicek described an equation relating the stroke volume (SV) to the change of impedance (dZ/dt), the ejection time (T) and a constant relating the resistivity of blood ρ, the distance between the electrodes (L) and the thoracic impedance (Zo):

$$SV = (\rho L^2/Zo^2) \times T \times dZ/dt \text{ max}$$

The circumstances during anaesthesia and surgery, with either depressed spontaneous ventilation, or with a paralysed patient in whom the artificial ventilation can be halted for a period of 10–15 s, provide the optimal conditions for measuring stroke volume by the thoracic impedance method. Under these conditions the Kubicek equation gives acceptable (±5%) es-

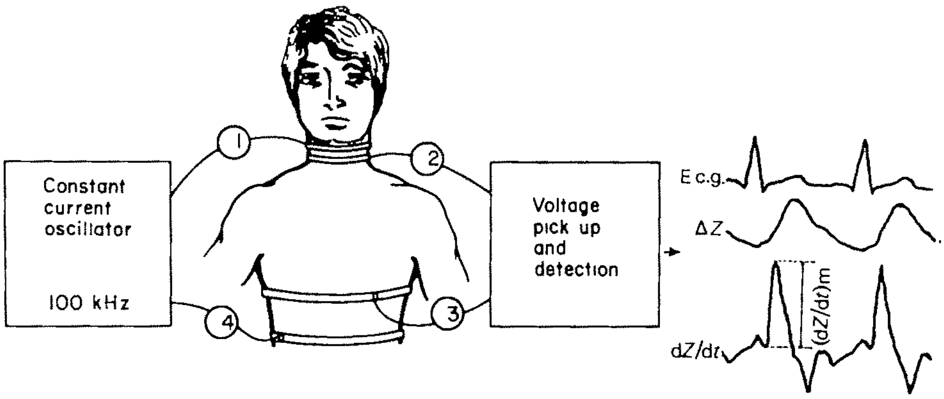

FIG. 6. Placement of the four mylar electrodes of the impedance cardiogram and the characteristic waveforms obtained. e.c.g. = electrocardiogram; ΔZ = change of impedance; dZ/dt = rate of change of impedance.

timates of changes of stroke volume, although the use of a standard value for ρ will yield inaccurate absolute values in patients who have different haematocrits (Hill, 1979).

As a non-invasive estimate of stroke volume, the transthoracic impedance cardiogram has advantages over most other methods and development of microprocessor-based computers should facilitate the on-line calculation of this variable.

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CORRESPONDENCE

CALIBRATION OF PEAK FLOW METERS

Sir,—Fisher and Shaw (1980) criticize the standard and Mini-Wright Peak Flow Meters (PFM) for not reading correctly when tested with their flow and volume calibrator (Shaw, Fisher and Hughes, 1979).

Had they read the paper by the late Dr C. B. McKerrow and myself (Wright and McKerrow, 1959) more carefully, they would have seen that their criticism is unjustified. We did not claim that the PFM measured air flow correctly in absolute units, but that it estimated, with sufficient precision for clinical purposes, the Peak Expiratory Flow (PEF) that the subject would produce when tested with an ideal instrument of negligible resistance and inertia. We obtained a calibration curve for this purpose by asking 20 subjects with widely varying PEF to blow alternately into a pneumotachograph and the PFM. This laborious and rather imprecise procedure was adopted because it was not technically possible to connect the two instruments in series. It was not clearly realized at the time that this is the *only* valid and satisfactory procedure. All portable, and most non-portable PFM have appreciable resistance or inertia, or both, and therefore modify the PEF to a varying extent. If they were calibrated to read the actual flow through them, the PEF of an individual would depend on the instrument used, which would be most unsatisfactory. As it is, any kind of PFM can be used to estimate the "ideal" PEF provided that it has been calibrated, either directly against an "ideal" instrument such as we used, or against an already calibrated instrument such as the Wright PFM. The latter procedure was adopted when calibrating the Minimeter (Wright, 1978; Oldham, Bevan and McDermott, 1979; Perks et al., 1979) and makes it possible to substitute the Mini for the Standard PFM without any confusion or appreciable loss of accuracy.

I do not, however, claim that our original calibration of the PFM was absolutely correct and it is open to anyone to repeat it. There are two sources of doubt. First, 20 subjects is a niggardly number on which to base the calibration of an instrument in world-wide use and a recalibration using a much larger number of subjects and a wider range of PEF, especially at the lower end of the scale, is long overdue. Second, the pneumotachograph we used had a resistance of only 15 mm H_2O at 700 litre min^{-1}, which was considered to be negligible compared with 120 mm H_2O for the PFM, but its steady flow calibration was carried out with a 1000-litre min^{-1} rotameter which had been calibrated on water and not on air. Fisher and Shaw's method could be used to obtain absolute calibration on air for flows up to 1000 litre min^{1} and I hope this will be done. If, as a result, our original calibration is found to have been seriously in error the Wright PFM will be adjusted accordingly. It must be remembered, however, that the estimate of PEF with secondary instruments is an inherently imprecise procedure. The resistance of the PFM modifies the PEF in different and unpredictable ways with different people. For example, the much higher resistance of the Minimeter does not usually reduce the PEF as much as would be expected, presumably because of the flexibility of the airways, whereas it has a marked effect on a rigid mechanical flow generator of the type used by Fisher and Shaw. In addition, low PEF cannot often be repeated because they exhaust the subject, so that calibration in this range will always be uncertain.

For the time being, therefore, and perhaps for ever, the Wright PFM scales will continue to be calculated as they are now.

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Sir,—We can assure Dr Wright that we did read his paper most carefully, but our paper was devoted to a constructive appraisal of meters in present use. However, Dr Wright has raised some points which should be clarified.

Meters are calibrated when their readings are compared with a known standard under the same measuring conditions. The tests described by Dr Wright only compare an individual meter with another instrument the dynamic calibration of which is also unknown. As each subject may not produce identical flows when blowing into the meter and reference instrument, standardization of measuring conditions is not achieved. Even if a large number of subjects are used, all that can be said is that the two instruments appear to give similar overall performances for that particular group. If healthy subjects are studied, it cannot be assumed that the correlation still holds good for those with respiratory deficiencies. Also, substantial discrepancies in performance may go undetected, for example at low flows.

There is no substitution for proper calibration, for this enables an instrument's performance to be defined in terms of accuracy and repeatability.

We cannot comment on the performance of the particular meters referred to in Wright's original paper. However, we did calibrate three of the original styled peak flow meters. For these meters the errors were fairly modest, being ±10% for flows greater than 150 litre min^{-1}. These errors were less than the errors for the 10 restyled and six mini-meters reported by us. This suggests a deterioration in the calibration over the years. What matters is the performance of currently produced meters. Our calibration allows a proper evaluation of this to be achieved.

Dr Wright suggests that it is all right to disguise the modifying effect of high resistance meters by alteration of the scale. This only leads to confusion and will prevent progress in our understanding of the important relationship between pressure and flow during the forced expiratory manoeuvre. It also breaks a fundamental law of the science of measurement: that units of measurement such as litre per minute should have an absolute definition and meaning.

Finally, Dr Wright states that the resistance of the meter has a marked effect on a rigid mechanical flow generator of the type used by us. This is untrue, for our calibration is independent of the resistance of the meter under test.

J. Fisher
A. Shaw
Glasgow

DOES KETAMINE METABOLITE II EXIST *IN VIVO*?

Sir,—In their review of the pharmacological properties of ketamine, Chang and Glazko (1974) postulated a tentative scheme for the biotransformation of this interesting anaesthetic agent (fig. 1). An N-demethylation, yielding nor-ketamine (MI) followed by a hydroxylation of the cyclohexane ring at two optional positions yields hydroxy-nor-ketamine (MIII and MIV, respectively). These two metabolites are then conjugated and excreted or dehydrated to dehydro-nor-ketamine (MII).

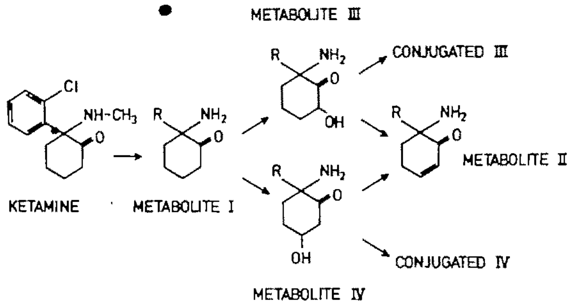

Fig. 1. Postulated biotransformation of ketamine according to Chang and Glazko (1974).

Following the work of Chang and Glazko, no further basic research on this topic has appeared in the literature. Their postulated scheme of biotransformation has been adopted and reappears, although enlarged, in a recent update by Zsigmond and Domino (1980). These authors postulated the presence of another dehydrated metabolite, dehydroketamine (MVII).

In our opinion, there are several reasons to question the *in vivo* existence of MII. Using the bioassay of Chang and Glazko (1972), we were not able to detect the presence of MII in cerebrospinal fluid, while simultaneously collected plasma samples (man or rat) contained easily determined concentrations of this compound (table I). These experiments included collections following prolonged anaesthesia times. In contrast, ketamine and MI were easily determined in c.s.f., with concentrations amounting to approximately 30–60% of those seen in plasma even within 15–20 min after induction of anaesthesia. Since there is no obvious reason to believe that MII should be less lipophilic or more strongly bound to plasma proteins than ketamine and MI, other explanations for this apparent "inhibited diffusibility" of MII across the blood–brain barrier have to be considered.

Table I. *Concentrations (µmol litre^{-1}) of ketamine, MI and MII in simultaneously collected samples of plasma and c.s.f. in five rats and one man during steady-state ketamine anaesthesia. n.d. = not detectable*

	Duration of anaesthesia (min)	Ketamine		MI		MII	
		C_{csf}	C_p	C_{csf}	C_p	C_{csf}	C_p
Man	20	2.8	4.5	0.2	0.6	n.d.	0.2
	60	5.6	9.4	0.9	1.9	n.d.	0.5
	180	6.5	11.0	1.8	3.4	n.d.	1.2
Rat							
1	15	30.3	44.4	1.5	4.4	n.d.	n.d.
2	20	21.3	41.3	1.6	3.8	n.d.	0.5
3	70	32.1	48.6	8.4	15.6	n.d.	7.5
4	90	33.8	52.5	13.1	25.0	n.d.	12.0
5	120	27.5	43.8	12.7	22.5	n.d.	14.2

The bioassay utilizes gas–liquid chromatography and includes benzene extraction of a strongly alkalized sample and subsequent derivatization with heptafluorobutyric anhydride in the presence of pyridine. Since alpha and betahydroxy-ketones such as MIII and MIV respectively (and possibly also their conjugates) would be expected to be converted easily to MII under the conditions described, and since there are reasons to believe that these less lipophilic compounds would diffuse slowly or not at all into the c.s.f., we believe there is a strong argument for considering MII as an artefact.

If MII does not exist *in vivo*, there is no obvious reason to postulate the presence of MVII.

If ketamine administration does not result in MII or MVII *in vivo*, man has never been exposed to these compounds unless given them directly. Consequently, during future research in this field, administration of MII and MVII to man should be carried out with extreme care.

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INHALATION OF GASTRIC CONTENTS

Sir,—We report two cases, one fatal, of aspiration pneumonitis following regurgitation and inhalation of gastric content during general anaesthesia for emergency evacuation of an incomplete abortion.

A 24-yr-old African female of average size was admitted at 09.00 h with a septic incomplete abortion. She received papaveretum 15 mg and atropine 0.6 mg i.m. at 14.00 h. The haemoglobin concentration was 10.5 g dl^{-1}. She had starved for 15 h. At 14.30 h the patient inhaled pure oxygen for 3 min through a Mapleson A system. Anaesthesia was induced at 14.40 h with Althesin 3 ml and diazepam 10 mg i.v. The patient developed severe laryngospasm. Suxamethonium 100 mg was injected i.v. to facilitate tracheal intubation. On direct laryngoscopy, approximately 15 ml of clear fluid was seen in the pharynx. After suction, a size 8 mm cuffed tracheal tube was inserted and the cuff inflated. Endotracheal suction before ventilation of the lungs revealed no obvious evidence of airway contamination. Anaesthesia was maintained with 50% nitrous oxide in oxygen with manual ventilation of the lungs; supplementary suxamethonium was given as required. Steroids were not administered and neither bronchoscopy nor bronchial toilet was performed.

At the end of anaesthesia, the patient was turned on her side and the tracheal tube removed. She was transferred to the recovery room, where she was observed for 2 h, breathing 40% oxygen though a Mix-o-mask. Auscultation of the lungs was normal and the patient returned to the ward breathing air at 17.20 h. Within 30 min the patient complained of shortness of breath and appeared distressed with sweating, tachycardia and hypotension. The level of consciousness deteriorated gradually despite the administration of supplementary oxygen by mask. Diffuse rales and bronchospasm were audible over the chest. The trachea was intubated with a cuffed Portex 8 mm endotracheal tube and the lungs ventilated mechanically. Chest x-ray showed the classic "snow storm" appearance consistent with a diagnosis of Mendelson's syndrome. Pa_{O_2} was 5 kPa (FI_{O_2} 0.6). PEEP, 5 cm H_2O, was given. Blood-gas and acid–base status improved and, together with her heart rate, central venous and arterial pressures, remained stable over the next 48 h. Chest x-rays showed some improvement of the lung condition.

Two days later Pa_{O_2} was 8.75 kPa (FI_{O_2} 0.6) and haemoglobin 9.6 g dl^{-1}. Two days later, Pa_{O_2} decreased dramatically to 3 kPa. FI_{O_2} was increased to 1.0 and PEEP from 5 to 10 cm H_2O. Despite these measures, the patient's condition deteriorated and she collapsed and died suddenly at 12.10 h, 5 days after admission to hospital. At postmortem examination, there was straw-coloured fluid present in the bronchi and a 3-cm embolus was discovered in the right ventricle and pulmonary artery. Death was attributed to massive pulmonary embolus complicating Mendelson's syndrome.

A 22-yr-old obese African woman was admitted to hospital in severe shock. There was a history of induced abortion using a salt and soap solution douche administered with a rubber pump. Following appropriate resuscitation and premedication with metoclopramide 10 mg i.v., the patient was transferred to the operating theatre, where general anaesthesia was induced with i.v. Althesin 5 ml and diazepam 10 mg, the patient having starved for at least 8 h.

On being placed in the lithotomy position, the patient regurgitated approximately 500 ml of green bile-stained fluid. The mouth, larynx and pharynx were suctioned under direct vision and a tracheal tube was passed, with subsequent endotracheal suction. A small Ryle's stomach tube was passed and suction applied with little result. The lungs were ventilated with pure oxygen. At termination of the operation, the patient was transferred to the critical care unit for observation, with a Ryle's tube in place. Air entry in the left lung was noted to be diminished. Twenty-four hours later, she was transferred to the ward, breathing air.

Subsequently the patient developed evidence of aspiration pneumonia, septicaemia and acute renal failure which responded to conservative treatment. Later she underwent total abdominal hysterectomy under general anaesthesia. A badly lacerated septic uterus was removed. After secondary suture of her abdominal wound 1 month later, again under general anaesthesia, she was discharged from the hospital two-and-a-half months after admission.

Regurgitation and aspiration of acid gastric content is well known in association with emergency obstetric anaesthesia, at or near term (Hodgkinson, 1980; Moir, 1980). The patients described here present a disturbing new facet, in that this complication arose in the early months of gestation. We have since adopted a policy that all women presenting for emergency uterine evacuation under general anaesthesia are managed in a manner similar to those presenting for Caesarean section, with the exception of routine endotracheal intubation (Brock-Utne and Downing, 1978; Buley et al., 1978).

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M. F. R. Khan
J. W. Downing
J. G. Brock-Utne
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Durban, South Africa

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OXYGEN FAILURE PROTECTION DEVICE

Sir,—In their description of a new oxygen failure protection device for use in anaesthetic apparatus (Flower, Naqvi and Woods, 1980) the authors state that it fulfils six of the seven principles advocated by Rosen and Hillard (1971), but that the requirement for operation by a gas supply only is "felt to be outdated in 1980". Unfortunately, the reasons for this view, for which the reader is referred to the introduction, appear to have been omitted, but I cannot agree that abandonment of this principle represents an advance in the specification or performance of an oxygen failure protection device. Though their design is fail-safe, electronic circuits and solenoids are not infallible and there will be times when an anaesthetic machine in good order is unusable for want of a battery. Rosen and Hillard's requirements are difficult, perhaps impossible, to achieve with a gas-operated device, but it is not clear how recommendations 2 (c) (i) and (ii) (inspired oxygen concentration not less than that of air; no increase in carbon dioxide concentration during either spontaneous or controlled breathing irrespective of breathing system in use) are met by this new device any more successfully than they are by existing designs. Devices such as those fitted by B.O.C. Medishield and Penlon to their anaesthetic machines work reliably, do not need to be switched on or off and are automatically tested during routine checking of the anaesthetic machine. The device proposed by Flower and his colleagues would not meet the requirements of the recently published Canadian criteria for anaesthetic machines (Canadian Standards Association, 1980) and is unlikely to conform to the proposed British and International standards.

J. D. Henville
Oxford

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Sir,—One of the main criticisms raised by Dr Henville was that the device would not meet the Canadian specification. Our device was made a considerable time in advance of that publication. However, as the requirements of "Standard" organizations of the different countries vary from country to country, it is very probable that the device in its present form would not comply to one or more standards. We feel, however, that the unit could be modified to meet any standard of any country.

For the sake of brevity we simply mentioned that the first principle of Rosen and Hillard, namely that the device be gas operated, was outdated in our opinion. In modern medicine many devices which are powered by electricity are used, for example, ventilator monitor alarms and dialysis machines, and we considered that an oxygen failure device powered by electricity was admissible. This gives us one very great advantage, in that we are able to detect a very small reduction in the oxygen supply pressure. All the safety devices which are operated by gas pressure alone give a warning of an impending failure when the supply pressure has already decreased by 60%, when failure is well established and the time available for rectification is very limited. An auditory alarm powered by electricity can be made as loud as required and is continuous until the fault has been rectified. In devices powered by the failing oxygen supply, the auditory alarm is weak and as the remaining oxygen expires so does the alarm. We considered that devices which are triggered and maintained by other gases, such as nitrous oxide were not worth comparison.

Finally, some devices already in use divert the anaesthetic gas supply from the patient in the event of failure and allow him to breathe theatre air. However, they have the disadvantage of using the anaesthetic gases to trigger the alarm and therefore those gases are vented to the theatre atmosphere. Our device contains all gases within its system, protecting the theatre staff and allowing the patient to be connected to the theatre environment.

K. A. Flower
Salford

PHARMACOKINETICS OF HIGH-DOSE FENTANYL

Sir—We read with interest the article by Bovill and Sebel (1980) as our work with much smaller doses of fentanyl confirms their findings.

Four patients undergoing elective cardiac surgery received fantanyl 5 µg kg^{-1} following induction of anaesthesia and normal plasma fentanyl concentration (PFC) decay curves were noted. Shortly before commencing cardiopulmonary bypass, which produced a mean haemodilution of 28%, each received a second dose of fentanyl 5 µg kg^{-1}. In three patients PFC was not detectable (less than 0.7 ng ml^{-1}) by the assay method used (Michiels, Hendriks and Heykants, 1977), 1–5 min after bypass. In the fourth patient, PFC decreased from 20 ng ml^{-1} immediately before bypass to 1 ng ml^{-1} after 5 min bypass. Thus although the proportional change in PFC can only be calculated for the last patient, it was always greatly in excess of a decrease caused by haemodilution.

Our plan of study differed from that of Bovill and Sebel in that a second dose of fentanyl was given and that bypass was initiated during the initial part of the decay curve, while fentanyl was being rapidly redistributed. In view of the great affinity of fentanyl for lung tissue (Hess, Herz and Friedel, 1971), PFC was measured in pulmonary artery blood samples from two patients as soon as bypass was established, and simultaneously with peripheral arterial samples. In both patients peripheral arterial PFC was too small to measure, but the pulmonary artery samples contained 1.4 ng ml^{-1} and 1.6 ng ml^{-1},—decreases of 85 and 53% from pre-bypass PFC. Thus, when fentanyl is given shortly before bypass, apparent disappearance from the circulation may be a result of sequestration within the lung.

We also observed a reappearance of fentanyl in the circulation during rewarming after hypothermic bypass to 28 °C. In the patient who was noted to have PFC of 1 ng ml^{-1} following bypass, the value was 2.2 ng ml^{-1} after 30 min rewarming. Another patient who had no measurable plasma fentanyl after bypass had a concentration of 1.3 ng ml^{-1} after 20 min rewarming. This may represent fentanyl previously sequestered in skeletal muscle during hypothermia (Hess, Herz and Friedel, 1971).

D. P. Cartwright
J. C. Chapman
J. R. Davies
A. M. Scoggins
Bristol

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PANCURONIUM AND NODAL RHYTHM

Sir,—Pancuronium has largely replaced tubocurarine because of its relative freedom from side-effects (McDowell and Clarke, 1969; Levin and Dillon, 1971). However, the drug may cause hypertension in some individuals (Fraley, Lemoncelli and Coleman, 1978). Cardiac arrhythmias, however, have been virtually unknown with pancuronium.

Recently, one of us (O. S.) has witnessed three cases of nodal rhythm directly related to the injection of pancuronium, and inquiries at another hospital in the region have revealed two more cases.

All of the patients were premedicated with morphine and either atropine or hyoscine. Anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen supplemented by either pethidine or droperidol–fentanyl. Before tracheal intubation, pancuronium (Pavulon, Organon) was given in a dose of 0.1 mg kg^{-1}. In all five patients, 1–2 min later the e.c.g. showed a change from sinus rhythm to nodal rhythm which reverted spontaneously after 20–90 s. (While the primary diagnosis of nodal rhythm was made from the oscilloscope, we managed in one case to register the arrhythmia on paper as well for accurate diagnosis.) In two of the patients, the nodal rhythm reappeared as a maintenance dose of pancuronium was given later. During the period of nodal rhythm, the arterial pressure was stable.

We have been unable to find any mention of this side-effect and would like to know, therefore, if any readers have seen a similar effect.

Olle Saemund
Eskil Dalenius
Falun, Sweden

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BOOK REVIEWS

Artificial Ventilation: Technical, Biological and Clinical Aspects. Edited by J. P. Payne and J. A. Bushman. Published (1980) by Academic Press, London. pp. 157; illustrated; indexed. Price £13.40.

For many years the Research Department of Anaesthetics at the Royal College of Surgeons of England has arranged regular symposia in which experts on various cardiorespiratory aspects of anaesthesia have spent a few days covering the topic in some depth. This is the edited proceedings of the latest of these symposia. It deals with mechanical ventilation, mainly in intensive therapy circumstances, looking at the present state of the art and speculating as to future developments.

The 12 contributions in this book cover different subject matter with little overlap. The contributors vary greatly in the approach to their material and therefore in the readers that they may interest. The editors, in a short preface, pick out four general aspects of ventilator therapy to which they claim the book is orientated, three of which are aimed firmly at the manufacturing and bioengineering fields. This emphasis is not, however, reflected in the rest of the book. Thus the chapter by Mapleson on the functional classification of ventilators is a concise and readable precis of his more detailed publications on this theme—good standard textbook material. Hayes briefly considers the problems of humidification and devotes most of his chapter to detailed descriptions of a number of currently available humidifiers. Such a "best buy" approach would be useful to anyone equipping an intensive therapy unit. Several chapters are specifically intended to guide the clinician in ventilator therapy. Adams, dealing with the physiological responses to IPPV, and Hanson in considering ventilation of the haemodynamically unstable patient, both give excellent, balanced reviews of topics that are too often dealt with in a more emotive fashion. Rivers, in the book's longest chapter, summarizes the physiological implications of ventilation of the newborn and gives didactic recommendations for the management of various resiratory problems in the neonate. McLaren gives a fascinating account of ventilatory problems in the land and air transport of the acutely ill.

A separate theme within the volume concerns the automatic control of artificial ventilation. Momtchiloff, in the opening chapter, deals generally with feedback control of ventilation and two approaches to computer-controlled artificial ventilation are discussed in the last two chapters of the book. These contributions are disappointing. Jonson and Prakash are enthusiastic proponents of the feedback control of artificial ventilation by end-tidal carbondioxide measurements. It is not difficult to conclude from their chapter that this approach, whilst easily applicable in subjects with healthy lungs and who therefore are unlikely to present great problems in ventilatory management, is unlikely to provide a generally applicable method of automatic control of ventilation. Bryan-Brown and his colleagues describe a computer-assisted approach to ventilatory management in which the computer spells out the steps along a rigid pre-defined procedure. Whilst this may be a useful teaching tool, their results show the limitations of this approach.

This is a well produced and adequately illustrated book. Covering, as it does, many different aspects of ventilator therapy, parts of it should interest a variey of readers. The clinician with little experience in the more difficult problems of ventilator therapy is the person likely to derive most from it.

C. M. CONWAY

Progress in Anesthesiology, Vol. 2. Molecular Mechanisms of Anesthesia. Edited by B. Raymond Fink. Published (1980) by Raven Press, New York. Pp. 510; illustrated; indexed. Price $65.96.

This volume is the proceedings of the fourth in a series of conferences organized and edited by Dr Fink, all held in Seattle and all devoted to fundamentals of the action of anaesthetic agents at the molecular and cellular level. The first conference took place in 1967 and was devoted to cellular and toxic actions of anaesthetics at a time when research workers were just beginning to take a serious interest in the field. It was published as *Toxicity of Anesthetics* (Williams and Wilkins, Baltimore) in 1968. The second conference, held in 1970, followed the same theme and was published in 1972 under the title *Cellular Biology and Toxicity of Anesthetics* (also by Williams and Wilkins). The direction then changed towards mechanisms of action, and the third Seattle conference held in 1974 was published in 1975 as *Progress in Anesthesiology, Vol. 1. Molecular Mechanisms of Anesthesia* (Raven Press, New York). The fourth and most recent conference held on June 14–17, 1979, followed the pattern of the third and the publication here reviewed is in the form of a second volume to the publication of 1975. (In passing it will be noticed how soon after the conferences Dr Fink is able to produce a polished volume of the proceedings.)

Most of the participants were from North America, with strong representation of anaesthetists, pharmacologists, physiologists and biophysicists. Anaesthetists, although the largest group, were actually in a minority although many papers and, indeed, many participants, were interdisciplinary. Specific sections were devoted to electrophysiology (introduced by Bertil Hille), neurochemistry (introduced by Julien Biebuyck) and physical chemistry (introduced by Jim Trudell). Other speakers included Drs Eger, Eyring, Kendig, Miller and, from the U.K., Bangham, Halsey and Richards. It is impossible to review the 35 major communications individually, but it may be said that all are at or near the forefront of our advancing knowledge on the mechanisms of narcosis. Additional material was in the form of 20 poster displays, which are reproduced in full. All types of anaesthetics are considered, including local anaesthetics.

The academic standard of the presentations is very high. Virtually all the studies which are described are fundamental and comparatively little of the content is directly relevant to the clinical practice of anaesthetics in the present state of our knowledge. Nevertheless, the proceedings of the symposium are the best and most up-to-date overview of the present state of knowledge in the fundamental actions of anaesthetics at the cellular and molecular level. It is essential reading for all engaged in this type of work and major departments of anaesthesia will need to have a copy for reference.

J. F. Nunn

Intensive Care for Nurses, 3rd edn. Edited by D. B. Clarke and A. D. Barnes. Published (1980) by Blackwell Scientific Publications. Pp. 195; illustrated; indexed. Price £6.75.

Previous editions of this book were published in 1971 and 1975. As before, all the authors are medical and the absence of a nursing contributor is a valid criticism in a book aimed at nursing staff—a point acknowledged in the Preface to the First Edition.

In addition to the usual topics of Intensive Care Nursing, this small paperback attempts to cover Coronary Care, Paediatric Intensive Care and Renal Dialysis and Transplantation. This is really too ambitious in a book of 195 pages and results in a rather superficial treatment of many aspects.

The Preface to this edition claims that there are major alterations to the text, but we found these to be relatively minor and the impression is gained that the more recent innovations in Intensive Therapy are not fully discussed.

The use of Intermittent Mandatory Ventilation (IMV) is covered only sketchily, and the advice to use increased dead-space in spontaneously breathing patients during weaning from ventilation is not to be welcomed. The recommendation to pump air into i.v. bottles to speed the rate of infusion is not one which would be easily defended. The complete absence of any references is disappointing.

This may prove a useful text for the inexperienced staff nurse or student nurse seeking an introduction to the subject, but would be of very limited value to those wishing to study intensive care nursing in more depth.

Isobel W. Cooper
J. G. Mone

Body Temperature Control in Anaesthesia, Surgery, and Intensive Care. By Anita Holdcroft. Published (1980) by Baillière Tindall. Pp. 179; illustrated; indexed. Price £8.50.

In view of the well-recognized changes in body temperature induced by anaesthesia, it is remarkable that this index is not monitored routinely by anaesthetists, especially as body temperature has been one of the prime variables faithfully recorded from all surgical patients by ward nurses. The importance of this lapse has been underlined by the ugly emergency of malignant hyperpyrexia (MH), yet although MH could provide the incentive, there is much more to be gained by temperature recording.

Anita Holdcroft has written a short but detailed account of body temperature, its control, variation and value in surgical patients and in victims of exposure. The book is easy to read and is well organized with clear and useful illustrations. References are kept to a minimum and are restricted largely to more notable contributions over the past four decades.

In the first chapter, which deals with physiological regulation of body temperature, the author has summarized many of the different hypotheses that have been used to explain this complex phenomenon. Her approach has been descriptive rather than mathematical, and she has ignored, perhaps wisely, the current accent on feedback mechanisms. It is unfortunate that the book was completed before the recent work on brown adipose tissue was reported, as this may provide a new dimension in the concepts of heat balance, even in adults.

This book should be read by all anaesthetists as it contains much of practical value and interest. It provides a clear rationale for temperature monitoring of all anaesthetized patients and will help to raise clinical standards.

F. R. Ellis

Basic Resuscitation and Primary Care. By F. Wilson and W. G. Park. Published by MTP Press Ltd. Pp. 339; illustrated; indexed. Price £9.95.

This well-produced book is aimed at the newly qualified doctor and senior nursing personnel. In the preface, the authors reveal at once that they are entirely hospital-orientated. Whilst this may be simple realism, to emphasize that "successful treatment during *the first* 60 minutes, and very often the first few minutes, is often vital in the saving of life", and then to ignore totally the movement towards pre-hospital care is a big disappointment.

Another general criticism is the use of the word "Basic" in the title. We are told that this is to emphasize that the apparatus is simple and available in all hospitals and that discussion will be limited to the first hour following treatment. The book kept to these limitations, but strays way beyond the concept of "basic" in its scope.

This reviewer found the layout difficult to follow. By dealing with specific conditions in the first section, the authors were faced with the choice of continually repeating themselves or omitting standard resuscitative procedures. Simple airway management does not appear until p. 203 and the advantages of the lateral or semi-prone position are ignored. Perhaps one of the problems of this book is its attempt to be all-embracing. The section on specific conditions ranges from cardiac arrest to malignant hyperpyrexia and from burns to pre-eclampsia. They are inevitably brief accounts, but nowhere are references given for further reading.

Section II is a useful and well-written chapter but, again, is largely out of place in a book entitled *Basic Resuscitation.* It contains chapters on anaesthetic equipment, ventilators, i.v. anaesthetics and neuromuscular blocking agents which seem to be beyond the scope of basic resuscitation and certainly beyond the scope of newly qualified doctors and senior nursing staff.

This is a disappointing book. The authors have much to contribute, but the contribution is made in a haphazard way to a wide variety of audience levels and without a coherent theme.

J. S. M. Zorab

Since this review was written, it has been learnt that Dr Frank Wilson died suddently at the beginning of this year. This is a sad loss to anaesthesia, to the Royal Lancaster Infirmary and to his family.

OTHER BOOKS RECEIVED

Le Foie en Anesthésie et en Réanimation. Journées d'enseignement post-universitaire de la Pitié-Salpetrière, 1979. Edited by C. Conseiller, J. M. Desmonts, P. Glaser, J. Montagne, G. G. Nahas, J. C. Salamagne, P. Viars and G. Vourc'h. Published 1980. Pp. 264; illustrated.

Curares et Curarisation. Journées d'enseignement post-universitaire de la Pitié-Salpetrière, 1979. Edited by C. Conseiller, J. M. Desmonts, P. Glaser, J. Montagne, G. G. Nahas, J. C. Salamagne, P. Viars and G. Vourc'h. Published 1980. Pp. 384; illustrated.

Antibiotiques et Réanimation Vasodilatateurs et Insuffisance Ventriculaire Gauche. Problemes actuels de réanimation, 1980. Edited by J. J. Pocidalo and F. Vachon. Published 1980. Pp. 328; illustrated.

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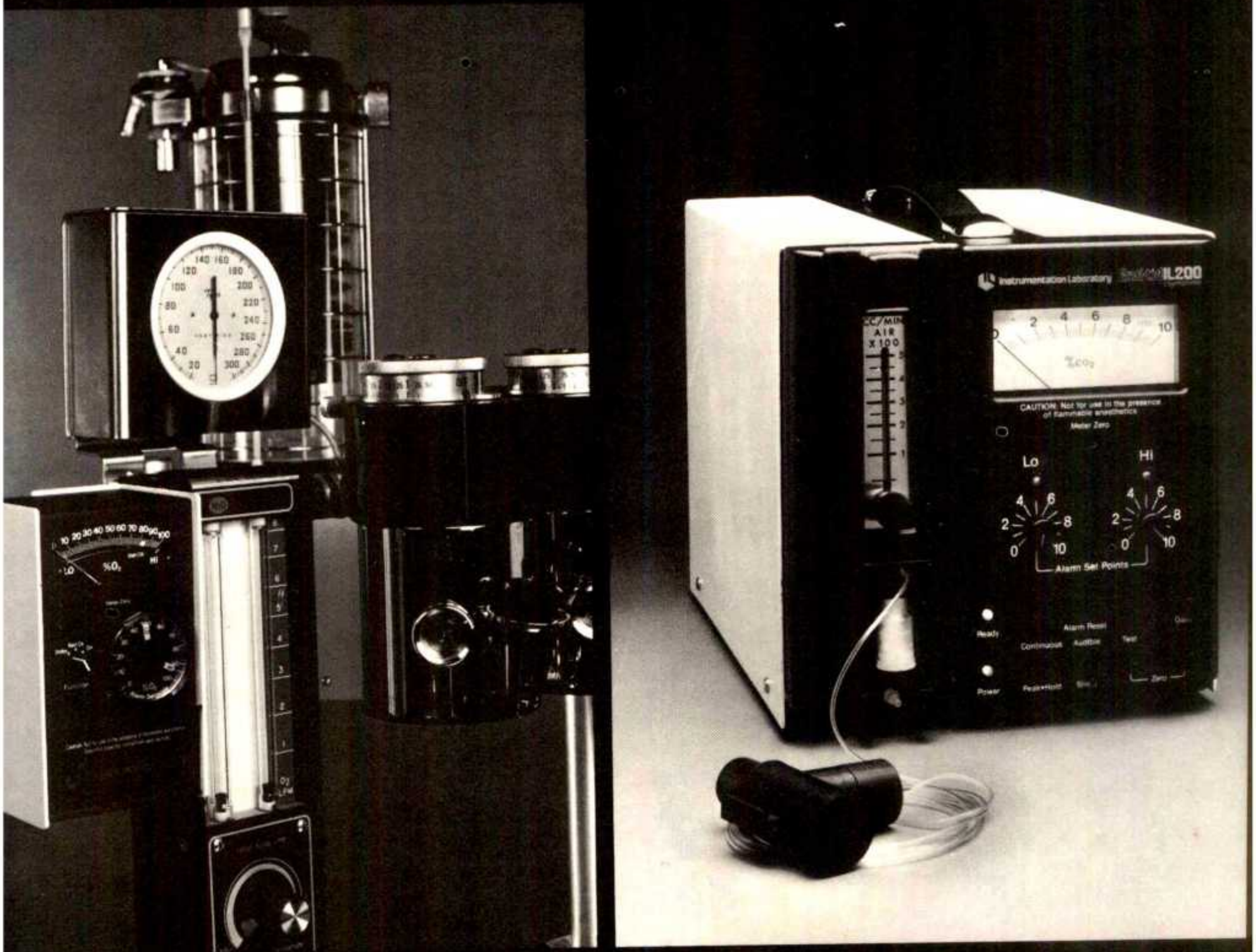

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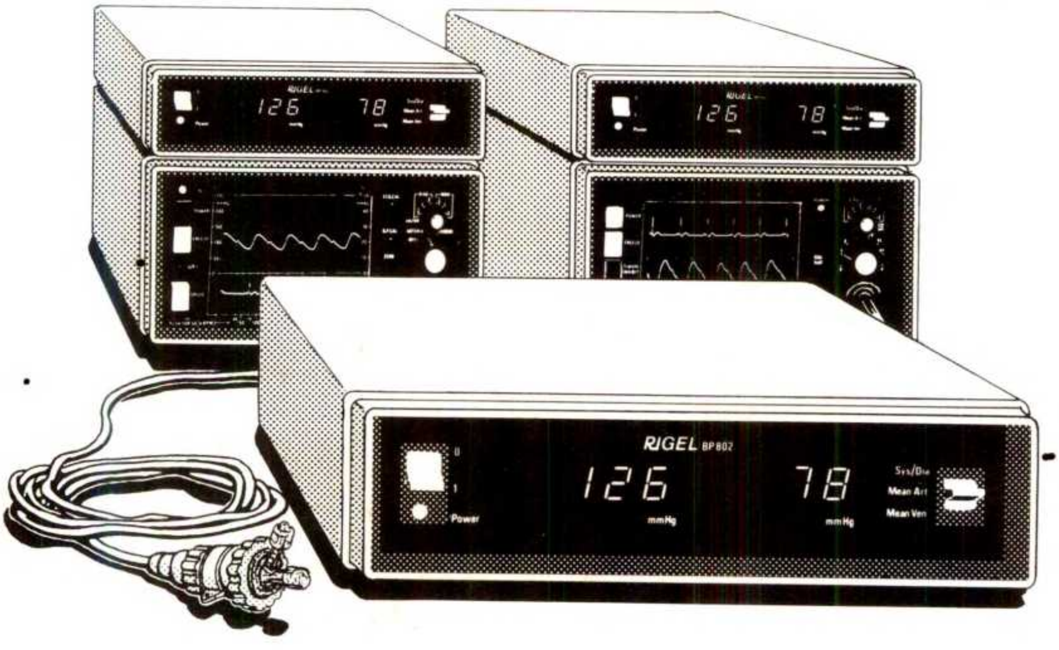

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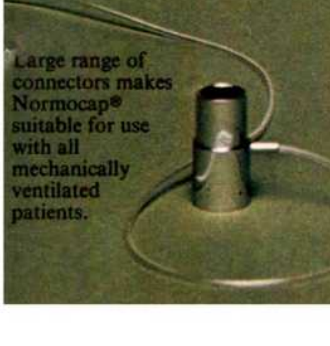

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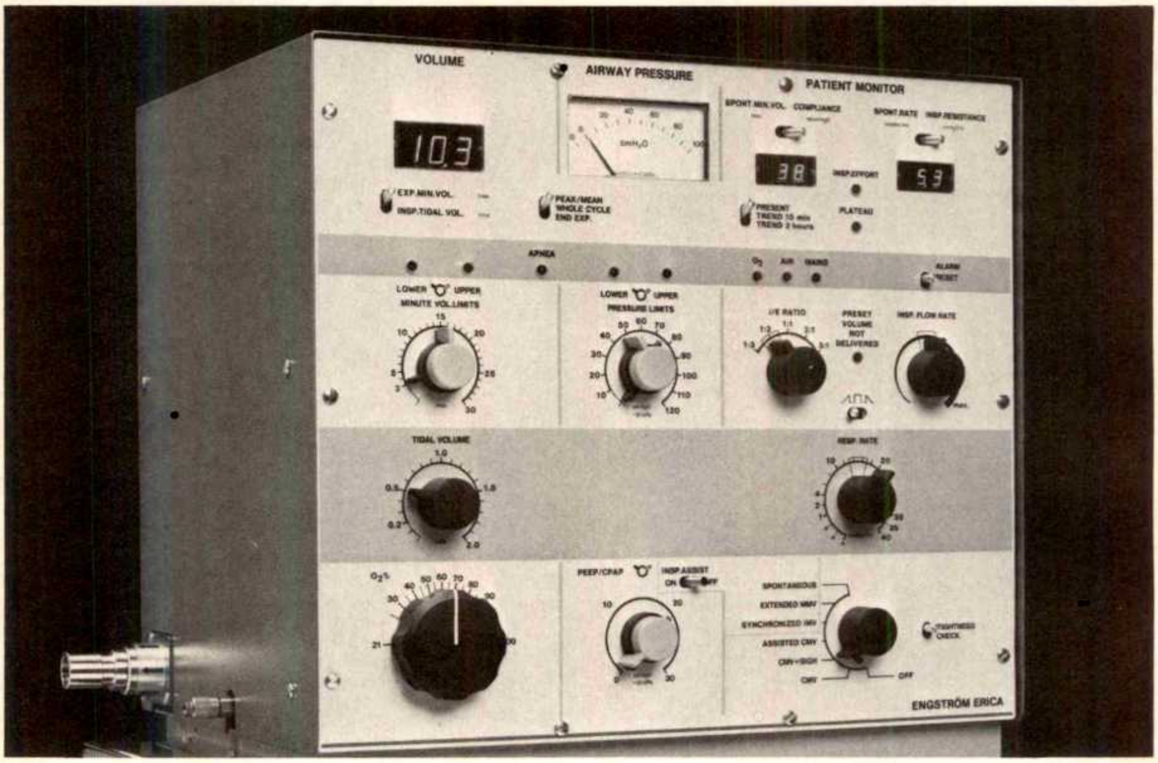

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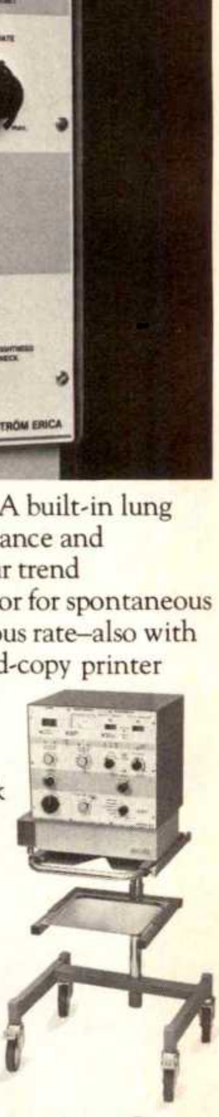

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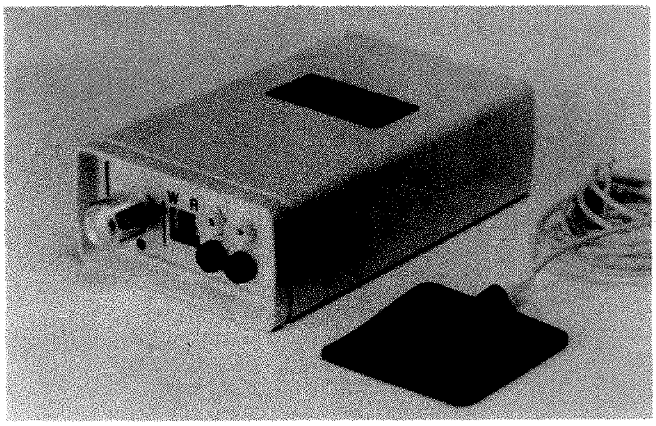

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Specification

Physical size: 33mm(H) x 68mm(W) x 110mm(L)

Weight: 190g

Output pulse: height 0 to 120 volts
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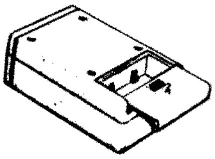
rate 15 to 150 pulses per second



Current consumption: 3.5mA from 9 volts

Power requirements: internal battery - a PP3 size rechargeable Ni-Cd (BEREC SB1166 or equivalent) is supplied with the unit and recommended but some 3 weeks of typical operation can be obtained from a dry PP3.

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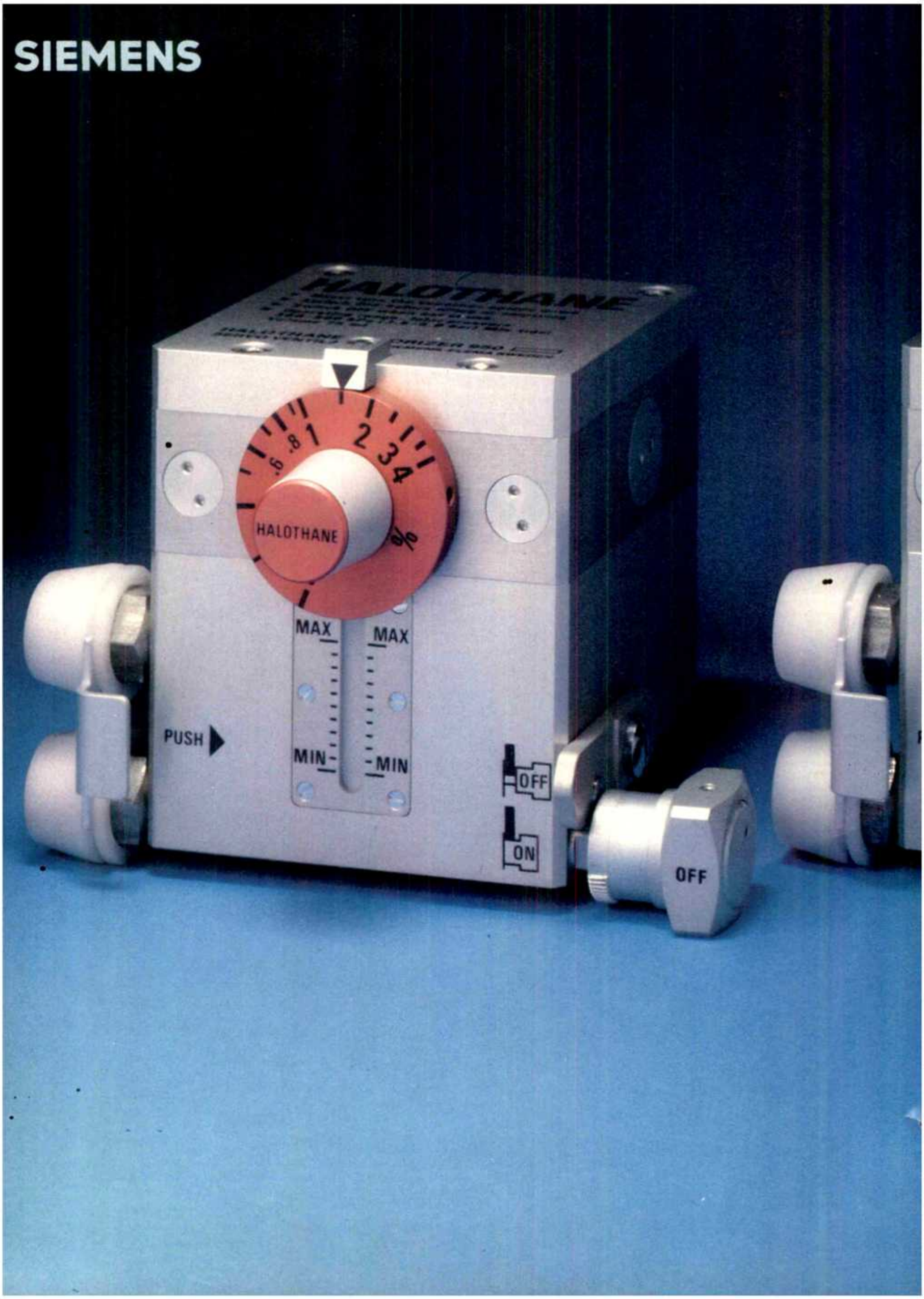
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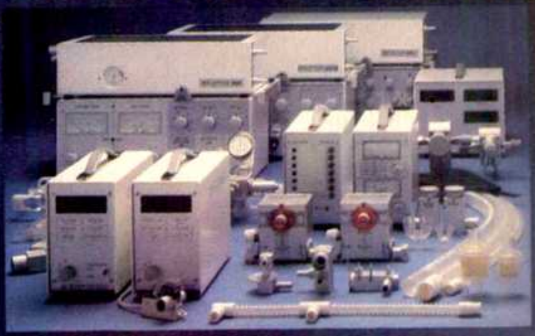

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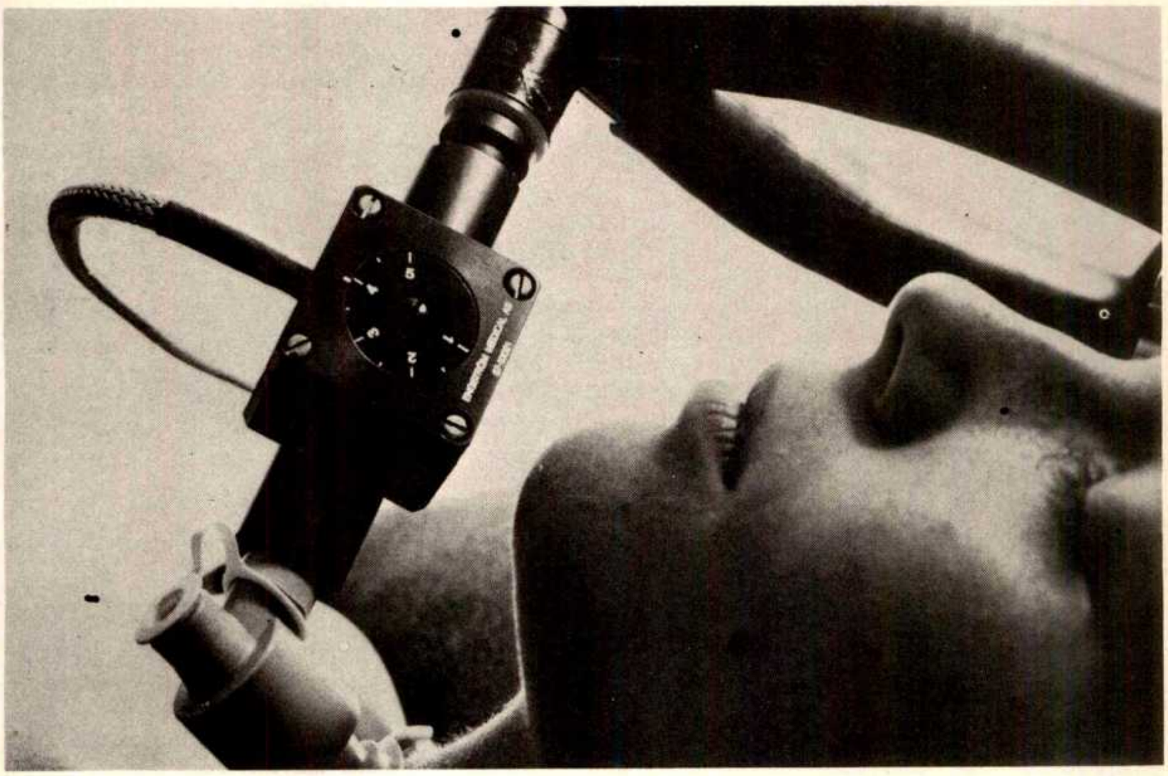

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be reduced to 5 minutes.

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 53, No. 8 AUGUST 1981

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EDITORIAL

SCIENTIFIC WRITING AND PEER REVIEW

In many countries of the world it is expected that the specialist anaesthetist seeking promotion to a senior appointment will offer evidence of capability in research and development related to the specialty. In the United Kingdom, for example, the Faculty of Anaesthetists and the Joint Committee on Higher Training of Anaesthetists give active encouragement to the provision of time for such activities, particularly in the case of Senior Registrars. The justification of this should not be disputed: apart from the obvious direct benefits which may accrue to our patients, the discipline required of a doctor in planning and executing a study and in the analysis and reporting of findings offers a unique measure of quality to complement what is known of his or her clinical competence and performance in diploma examinations. The manner in which the research work is undertaken is as important as, and in some respects more important than, the significance of the development or discovery. Thus there is a need for some type of peer review of the scientific report.

Traditionally there are three ways in which this peer review can be achieved: oral presentation to a learned society, the examination of a thesis and assessment in anticipation of publication in a learned journal. (The review of a submission to a fund-granting agency might be regarded as a fourth method, but this is an unlikely possibility in the absence of one or more of the other three.)

Oral presentation, while often an invaluable preliminary to the preparation of a written record, is the most fickle approach to peer review, the quality of which will depend on the competence and mood of those present, the clarity of presentation and the opportunities for discussion.

The examination of a thesis is perhaps the best method of review, since it allows full and detailed consideration of the candidate's background knowledge, the methods of study, analysis of data, discussion of the findings and their implication. However, the scope and requirements normally expected of candidates for the degrees of M.D. or PH.D. (the awards sought most commonly by anaesthetists in the U.K.) are often greater than the senior trainee in anaesthesia will be able to offer.

Thus the journal is the mainstay of peer assessment of research, and those periodicals which publish correspondence afford an additional dimension in review. There are signs, however, that this function of journals may become overloaded, and it is time to examine alternatives. In recent years this Journal, in common with many of our contemporaries, has enjoyed a substantial increase in the number of proffered manuscripts. This is a reflection of the widely accepted fact that the academic standing of the specialty continues to improve. Perhaps it reflects also fiercer competition for promotion in clinical and academic posts and for research funds. Whatever the reasons, the result is bound to be greater competitiveness for acceptance for publication and inevitable casualties. The apparent solution of increasing the size of existing journals or creating new ones would be difficult to justify at a time when increasing production and distribution costs are already placing a heavy burden on subscribers, not least institutional libraries.

There is a feeling among editors that some of the casualties involve research reports which seem to have been brought to fruition, as regards suitability for publication, prematurely in order to fulfil the need for peer review, and it is reasonable to ask if a return to the thesis may not offer a better alternative which will meet the aspirations of the author. The customary regulations for a Mastership degree in British universities would allow competent review of a research report while the traditional "taught" element of the course might be designed to meet the requirements of the trainee clinician in offering a programme of instruction in research methods, data processing and analysis, and in scientific reporting.

It is not our intention to deflect material that is fit to publish from the printed page to the archives of our universities. On the contrary, it might be hoped that the development of research reporting along the lines indicated would allow the journals to develop their appropriate role as a vehicle for mature, perhaps composite, reporting. In this way the interest in the printed page for the reader would be increased while the greater involvement of Universities in encouraging and improving the quality of research by clinicians would be to the benefit of all.

Alastair A. Spence

Br. J. Anaesth. (1981), 53, 785

INTERACTIONS BETWEEN THE NEUROMUSCULAR BLOCKING DRUG ORG NC45 AND SOME ANAESTHETIC, ANALGESIC AND ANTIMICROBIAL AGENTS

I. C. McINDEWAR AND R. J. MARSHALL

SUMMARY

The effects of some anaesthetics and other agents used in anaesthetic practice on the neuromuscular blocking activity of cumulative doses of Org NC45 have been studied in cats anaesthetized with chloralose. As expected from studies with other neuromuscular blocking drugs, both inhalation and i.v. anaesthetics reduced the doses of Org NC45 required for neuromuscular blockade. An apparently specific potentiating interaction between Org NC45 and metronidazole was observed.

Org NC45, 1-[(2β,3α,5α,16β,17β)-3,17-bis-(acetyloxy)-2-(1-piperidinyl)-androstan-16-yl]-1-methyl-piperidinium bromide is a new non-depolarizing neuromuscular blocking agent (Durant et al., 1979) which shows considerable promise as a muscle relaxant for use during clinical anaesthesia (Krieg, Crul and Booij, 1980). Several anaesthetic agents and certain other drugs that might be administered concurrently have been shown to potentiate non-depolarizing neuromuscular blocking drugs (Miller, 1975; Ngai, 1975; MacLagan, 1976; Bowman, 1980). This study was undertaken to determine if similar interactions occur with Org NC45. Metronidazole was included for study because it is often used prophylactically to protect against bacteroides infections (Willis et al., 1977) and systemic gram negative bacterial infections following operations on the colon or uterus (Darrell and Uttley, 1976).

METHODS

Cats of either sex, weighing 1.8–3 kg, were anaesthetized with a mixture of 1% α-chloralose 8 ml kg^{-1} and pentobarbitone sodium 5 mg kg^{-1} injected i.p. This method of anaesthesia was chosen because in previous unpublished experiments it was found that, in decerebrate cats, neuromuscler blocking drugs produced the same effects when injected before and after the administration of this chloralose–pentobarbitone mixture.

The lungs were artificially ventilated throughout the experiments with air 15–20 ml kg^{-1} at 28 b.p.m. (Palmer respirator, model 16/24). Respiratory volume was adjusted to maintain arterial pH at 7.42±0.02.

The gastrocnemius–soleus muscle group of the left hindlimb was freed from other tissues and the Achilles tendon was severed about 1 cm above its insertion into the calcaneous and attached to a Grass force displacement transducer (model FT03). The limb was immobilized by a drill placed through the head of the tibia. A resting tension of 30 g was applied to the muscle and maximal twitches evoked by stimulating the sciatic nerve in the popliteal space with rectangular pulses of 0.2 ms duration from a Grass (model S8) stimulator at twice the strength necessary to evoke a maximal twitch. Bipolar platinum electrodes were used and the sciatic nerve trunk was ligated and cut central to the electrodes. The frequency of stimulation was 0.1 Hz. The nerve and muscle were bathed in heavy liquid paraffin B.P. and the animal's body temperature was maintained at 37±0.5 °C. Arterial pressure was recorded from a carotid artery with a Bell & Howell pressure transducer. The transducers were coupled to appropriate Ormed preamplifiers and records of muscle contraction and arterial pressure displayed simultaneously on an Ormed M4 polygraph.

Drugs were injected through a cannula placed in an external jugular vein and washed in with 0.9% w/v sodium chloride solution 2 ml containing heparin 2500 i.u. litre^{-1}. Inhalation anaesthetics were administered in oxygen at a total flow of 2 litre min^{-1}. The anaesthetic apparatus was a Penlon P.I.S.A.M. trolley with an O.M.V. 50 vaporizer and interchangeable calibrated discs for each of the anaesthetics used.

I. C. McINDEWAR, L.I.BIOL.; R. J. MARSHALL, B.SC., PH.D.; Department of Pharmacology, Organon Laboratories Limited, Newhouse, Lanarkshire ML1 5SH.

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The drugs and formulations used were Org NC45 (1-[2β,3α,5α,16β,17β)-3,17-bis(acetyloxy)-2-(1-piperidinyl)-androstan-16-yl]-1-methylpiperidinium bromide) (Organon), metronidazole (Flagyl, May & Baker), halothane (I.C.I.), enflurane (Abbott), methoxyflurane (Abbott), cyclopropane (B.O.C.), nitrous oxide (B.O.C.), Althesin (Glaxo), propanidid (Bayer), ketamine (Parke-Davis), methohexitone (Lilly), sodium thiopentone (Boots), etomidate (Janssen), sodium oxybate (E.G.I.C.), chlorpromazine (May & Baker), Crystamycin (Glaxo), diazepam (Roche), morphine (BDH) and Thalamonal (Janssen). Sodium oxybate is the sodium salt of gamma-hydroxybutyric acid.

Statistical evaluation of results

The data were analysed by regression analysis and doses of neuromuscular blocking drug necessary to produce 50% twitch block under different conditions were obtained using a least squares linear regression technique. The doses were compared using Student's paired t test. Where this analysis showed a significantly different result, the degree of potentiation was assessed as the dose ratio. The total degree of blockade was compared using the paired t test and only with methohexitone was this found to be significantly different from control. Hence the recovery times of all drugs tested except methohexitone 10 mg kg^{-1} could be compared. The recovery times for 25 to 75% recovery and maximal block to 90% recovery were measured in minutes and compared using the paired t test. Where significant differences were found, the percentage increase in the recovery time was calculated. Onset times could not be calculated because of the cumulative method of drug injection used.

Neuromuscular block was assessed by constructing cumulative log dose–response curves as shown in figure 1. An initial priming dose of Org NC45 15 μg kg^{-1} was injected and this was followed by incremental doses of 5 μg kg^{-1}, each administered at the time of maximal block produced by the preceding dose. The increments were repeated until an 85–90% depression of the twitch was produced, after which spontaneous recovery was allowed to occur. The incremental doses were small because of the steepness of the dose–response curve. The percentage twitch depression was then plotted against the log of the sum of the doses. In preliminary experiments in nine cats, four such cumulative administrations of Org NC45 were made in each. In all cases, an interval of 1 h was allowed between the point of full recovery from one and the start of the next cumulative injection pattern. The results showed that, under these conditions, there was no significant difference between the depths of block produced each time. In any one cat, the four cumulative dose–responses were virtually superimposable. The combined results are summarized in figure 4A.

When testing for possible interactions, two control cumulative responses to Org NC45 were first determined (60-min interval as described above). The agent under test was then administered i.v. or by inhalation before the start of the third cumulative response to Org NC45. Any arterial pressure changes produced by inhalation anaesthetics were allowed to stabilize before the injection of Org NC45. Administration of inhalation anaesthetics was continued throughout the cumulative injection of Org NC45 and until the twitch height had recovered to 85–95% of the control amplitude. Metronidazole was given as an i.v. infusion over 20 min, ending 5 min before the start of the cumulative administration of Org NC45. The plan of study is illustrated with Althesin in figure 1. One hour after full recovery, a

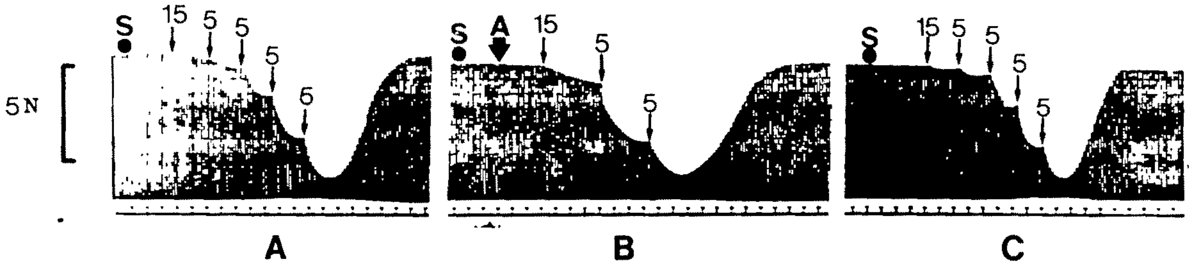

FIG. 1. Effects of cumulative administration of Org NC45 (μg kg^{-1}, at the arrows) on twitches of the gastrocneumius muscle before (A), immediately after (B) and 75 min after (C) the administration of Althesin 0.1 mg kg^{-1} i.v. (at large arrow, A).

further cumulative response to Org NC45 was determined and a final response determined after a similar interval. Except when metronidazole was the drug under study, the curve determined 60 min after the first interaction curve was hardly distinguishable from the response determined before administration of the drug under test (fig. 1). The control curve was therefore constructed from the mean of these two determinations (the mean of panels A and C, in figure 1). The test curve was that determined in the presence of the potential interacting drug (panel B of figure 1). The results of the experiment shown in figure 1 are plotted in figure 2 to illustrate the method. The results of all experiments were plotted individually in this way and the mean potentiation factors were calculated from the shift of the curves at the level of 50% twitch block. In all cases, when a shift occurred, it was parallel and to the left, indicating potentiation.

RESULTS

Inhalation anaesthetics

The effects of halothane, enflurane, methoxyflurane, cyclopropane and nitrous oxide on the neuromuscular blocking activity of and recovery rates from Org NC45 are shown in table I. Halothane and enflurane caused a significant shift to the left of the dose–response curve for Org NC45 only at the larger concentration of 2%, with no shift at the smaller concentration. Methoxyflurane at 0.3% and 0.6% significantly potentiated the neuromuscular blocking action of Org NC45.

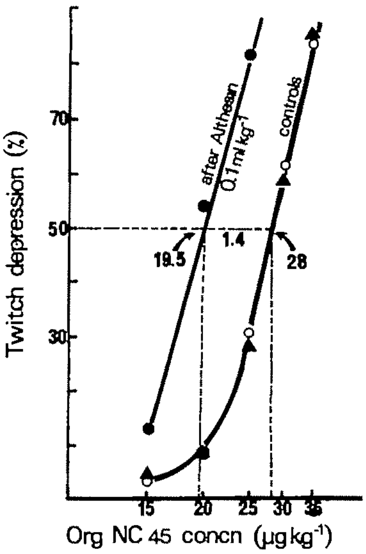

FIG. 2. Concentration–effect curves for Org NC45, before (○) immediately after (●) and 90 min after (▲) the adminstration of Althesin 0.1 mg kg^{-1} i.v., showing how the dose ratio was calculated. In this experiment (shown in figure 1) Althesin potentiated the effects of Org NC45 by a factor of 1.4.

All three volatile agents significantly increased the time from 25 to 75% recovery and from maximum block to 90% recovery. Cyclopropane and nitrous oxide had no effect on either the depth of block produced by Org NC45 or the rate of recovery. None of the inhalation anaesthetics alone produced any change in the amplitude of the muscle twitches.

TABLE I. *Potentiation of Org NC45 by inhalation anaesthetics in the cat. All anaesthetics given in oxygen 2 litre min*$^{-1}$. $^{*}P<0.05$; $^{**}P<0.01$; $^{\dagger}P<0.02$; $^{***}P<0.001$

Drug	Dose	*n*	Degree of potentiation	Consequent proportion of normal dose of Org NC45 for same effects	Percentage increase in recovery time	
					25–75%	0–90%
None	—	10	1.05±0.04	—	4±5	4±4
	—	9	1.04±0.02	—	6±6	4±6
Halothane	1%	5	n.s.	100%	n.s.	n.s.
	2%	6	1.33±0.05**	75%	43±8**	31±10*
Enflurane	1%	6	n.s.	100%	46±14†	n.s.
	2%	7	1.40±0.08***	71%	76±32†	52±20**
Methoxyflurane	0.3%	6	1.24±0.08	81%	32±7†	n.s.
	0.6%	5	1.40±0.07***	71%	75±11**	51±11**
Cyclopropane	10%	5	n.s.	100%	n.s.	n.s.
	20%	5	n.s.	100%	n.s.	n.s.
Nitrous oxide	50%	6	n.s.	100%	n.s.	n.s.
	80%	6	n.s.	100%	n.s.	n.s.

Intravenous anaesthetics

The effects of Althesin, propanidid, ketamine, methohexitone, thiopentone sodium, etomidate and sodium oxybate on the neuromuscular blocking activity of and the recovery rates from Org NC 45 are shown in table II. All i.v. anaesthetics tested potentiated the blocking action of Org NC 45. In contrast to the inhalation anaesthetics, only ketamine had any effect on the recovery time and even this effect was very small. None of the i.v. anaesthetics themselves affected the amplitude of the muscle twitches.

Other interacting agents

The effects of chlorpromazine, benzylpenicillin plus streptomycin (Crystamycin), diazepam, morphine, droperidol with fentanyl (Thalamonal) on the neuromuscular blocking activity and recovery rates of Org NC 45 are given in table III. Chlorpromazine $5\,mg\,kg^{-1}$ and $10\,mg\,kg^{-1}$ caused slight potentiation of the neuromuscular blocking effect of Org NC 45 which, surprisingly, was statistically significant only with the smaller dose. The streptomycin–benzylpenicillin mixture caused a significant potentiation of the neuro-

TABLE II. *Potentiation of Org NC 45 by i.v. anaesthetics in the cat. n.s. = $P > 0.05$ (paired* t *test); n/a = not applicable (see method); *$P < 0.05$; †$P < 0.02$; **$P < 0.01$; ***$P < 0.001$*

Drug	Dose	*n*	Degree of potentiation of ED$_{50}$ (±SEM)	Consequent proportion of normal dose of Org NC 45 for same effect	Percentage increase in recovery time 25–75%	Percentage increase in recovery time 0–90%
Althesin	$0.05\,ml\,kg^{-1}$	5	n.s.	100%	n.s.	n.s.
	$0.1\,ml\,kg^{-1}$	5	1.33±0.07**	75%	n.s.	n.s.
Etomidate	$2\,mg\,kg^{-1}$	7	1.12±0.03**	89%	n.s.	n.s.
	$4\,mg\,kg^{-1}$	6	1.24±0.04***	81%	n.s.	n.s.
Ketamine	$5\,mg\,kg^{-1}$	6	1.31±0.04**	76%	12±4†	13±5*
	$10\,mg\,kg^{-1}$	5	1.39±0.05***	72%	n.s.	24±8*
Methohexitone	$5\,mg\,kg^{-1}$	7	1.30±0.08**	77%	n.s.	n.s.
	$10\,mg\,kg^{-1}$	6	1.58±0.10**	63%	n/a	n/a
Propanidid	$5\,mg\,kg^{-1}$	5	1.34±0.04***	75%	n.s.	n.s.
	$10\,mg\,kg^{-1}$	5	1.63±0.08**	61%	n.s.	n.s.
Thiopentone	$5\,mg\,kg^{-1}$	4	n.s.	100%	n.s.	n.s.
	$10\,mg\,kg^{-1}$	4	1.30±0.07*	77%	n.s.	n.s.
Sodium oxybate	$40\,mg\,kg^{-1}$	5	n.s.	100%	n.s.	10±4*
	$60\,mg\,kg^{-1}$	4	1.18±0.06*	85%	n.s.	n.s.

TABLE III. *Potentiation of Org NC 45 by other agents in the cat. n.s. = $P > 0.05$ (paired* t *test). * $P < 0.05$; †$P < 0.02$; **$P < 0.01$; ***$P < 0.001$. ‡Benzylpenicillin 300 mg + streptomycin 500 mg; §fentanyl 50 µg + droperidol $2.5\,mg\,ml^{-1}$*

Drug	Dose	*n*	Degree of protentiation of ED$_{50}$ (±SEM)	Consequent proportion of normal dose of Org NC 45 for same effect	Percentage increase in recovery time 25–75%	Percentage increase in recovery time 0–90%
Chlorpromazine	$5\,mg\,kg^{-1}$	5	1.14±0.05*	88%	12±5	n.s.
	$10\,mg\,kg^{-1}$	5	n.s.	100%	n.s.	n.s.
Crystamycin‡	$6\,mg\,kg^{-1}$	7	1.42±0.11***	70%	n.s.	n.s.
	$32\,mg\,kg^{-1}$	4	1.38±0.03***	72%	n.s.	n.s.
Diazepam	$2\,mg\,kg^{-1}$	5	n.s.	100%	n.s.	n.s.
Morphine	$1\,mg\,kg^{-1}$	5	n.s.	100%	n.s.	11±3†
	$2\,mg\,kg^{-1}$	5	n.s.	100%	n.s.	10±1**
Thalamonal§	$0.15\,ml\,kg^{-1}$	5	n.s.	100%	n.s.	n.s.
	$0.25\,ml\,kg^{-1}$	5	n.s.	100%	n.s.	15±5*

muscular blocking activity of Org NC45 ($P<0.001$) without any effect on recovery time.

Metronidazole

No interaction was evident when metronidazole 1 mg kg^{-1} min^{-1} was infused for 20 min immediately before the cumulative administration of Org NC45. However, a marked potentiation was evident after a further 1 h, even though the metronidazole infusion had been terminated about 70 min earlier. This effect is illustrated in figure 3 and the combined results of five other cats are presented as a histogram in figure 4B. The potentiations in the experiment shown in figure 3 and in one other experiment were so marked that it was not possible to construct dose–response curves. The results of these two experiments are not included in figure 4B. Although the block was augmented in all seven cats, there was no significant change in the recovery rates (25–75% twitch recovery).

In a further series of experiments on six cats, pancuronium was used in place of Org NC45. Metronidazole was without statistically significant effect on the neuromuscular block produced by pancuronium as indicated in figure 4C. The effect of metronidazole therefore appeared to be specific to Org NC45.

DISCUSSION

The interaction between neuromuscular blocking drugs and anaesthetic agents was well recognized shortly after tubocurarine was introduced to anaesthetic practice. In contrast to most previous *in vivo* interaction studies (Bonta, Goorissen and Derkx, 1968; Krieg et al., 1980), we have utilized a cumulative dose–response method to enable the investigation of interactions on the whole dose–response curve of the neuromusclar blocking drug as opposed to interactions with single doses or infusions. This consequently enabled measurement of the degree of potentiation in terms of the reduction in the required dose of the blocking drug. Since redistribution and metabolism occur continuously, cumulative adminstration would result in overestimation of effective doses of Org NC45, and the method cannot be used to deduce, for example, the true 50% bolus blocking dose. However, the method is valid for comparing dose–response curves in the presence and absence of potential interacting agents.

In this study, halothane, enflurane and methoxyflurane in concentrations within the clinical range all significantly reduced the concentrations of Org NC45 required for neuromuscular blockade and prolonged recovery from the drug. The newer fluorinated ethers, methoxyflurane and

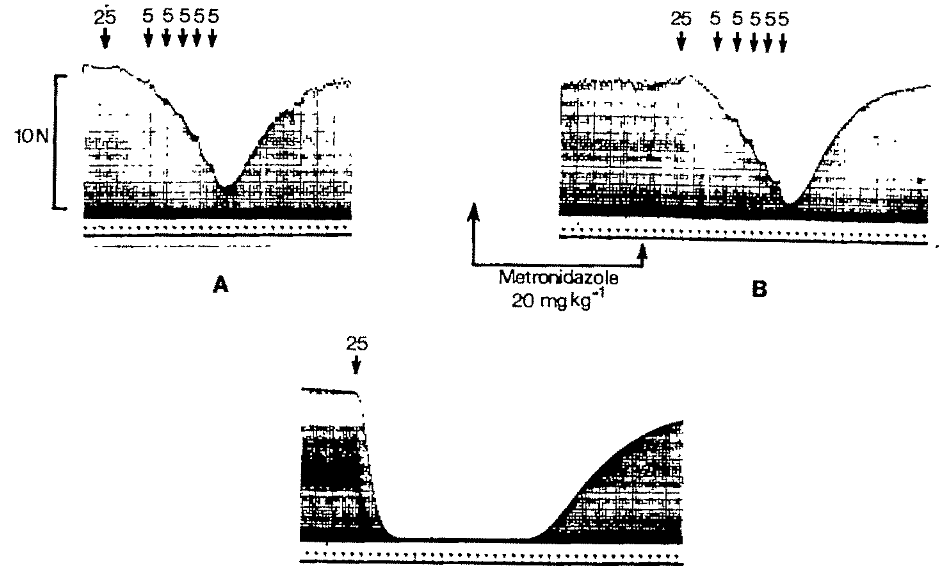

FIG. 3. Cumulative concentration–effect curves to Org NC45 before (A), 5 min after (B) and 75 min after (C) the infusion of metronidazole 20 mg kg^{-1} i.v. The bolus concentrations of Org NC45 (at the arrows) are expressed in µg kg^{-1}. Time markers = 1 min.

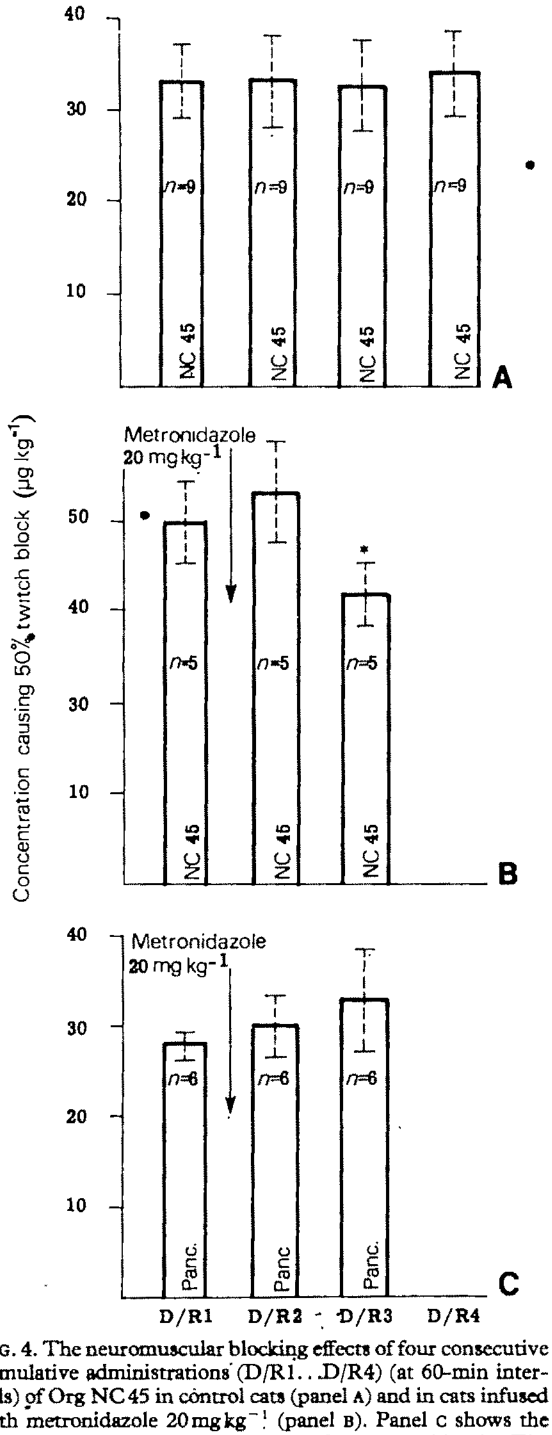

FIG. 4. The neuromuscular blocking effects of four consecutive cumulative administrations (D/R1...D/R4) (at 60-min intervals) of Org NC 45 in control cats (panel A) and in cats infused with metronidazole $20\,mg\,kg^{-1}$ (panel B). Panel C shows the effects of pancuronium before and after metronidazole. The neuromuscular blocking activity is expressed on the ordinate as the mean concentration causing 50% twitch blockade. $^{*}P < 0.05$, compared with pre-metronidazole value.

enflurane, were more potent than halothane, which agrees with previous experimental and clinical observations using tubocurarine as relaxant (Lebowitz, Blitt and Walts, 1970; Waud, 1979). In contrast, the concentrations of both cyclopropane and nitrous oxide used in this study did not modify the neuromuscular blocking actions of Org NC 45. Both of these anaesthetic agents have been shown to facilitate slightly, rather than depress, neuromuscular transmission (Watland et al., 1957; Sabawala and Dillon, 1958; Ngai, Hanks and Farhie, 1965), and therefore they might not be expected to potentiate the effects of neuromuscular blocking agents.

In the doses used, the i.v. anaesthetic agents tested also reduced the dose of Org NC 45 necessary for neuromuscular blockade but, in contrast to the inhalation anaesthetics, this potentiation was not accompanied by an increase in recovery times except in the case of ketamine. This latter finding agrees with the recently published findings of Krieg and others (1980) who used single bolus injections of Org NC 45 in anaesthetized cats and rats.

The doses of Althesin, propanidid and sodium oxybate found to potentiate Org NC 45 were similar to doses used clinically. The effective doses of thiopentone and ketamine were greater and the doses of etomidate and methohexitone used were considerably greater. It seems, therefore, that a significant interaction might be likely only with Althesin, propanidid and sodium oxybate, and even with these the potentiation was not great.

Diazepam, morphine and the mixture of fentanyl and droperidol were without effect on the blocking action of Org NC 45. Chlorpromazine produced some potentiation but only in a large dose i.v. and the interaction is therefore probably not important in practice. The potentiating effect of Crystamycin (benzylpenicillin plus streptomycin) was probably entirely caused by streptomycin, since penicillins have been found to be inactive (Singh, Harvey and Marshall, 1978), and the depressant effect of streptomycin and other aminoglycosides on neuromuscular transmission is well documented (Bowman, 1980).

The purpose of this investigation was to test for potential interactions; no evidence was sought with regard to the potentiating mechanisms which might occur at the neuromuscular junction or be secondary to pharmacokinetic modification or to blood flow changes.

The potentiation of the effects of Org NC45 produced by metronidazole was not apparent 10min after administration, but was observed clearly after 1 h. As far as we are aware, this is the first report of a potentiating interaction between metronidazole and a neuromuscular blocking drug. The unusual time course of the interaction and the observation that no such interaction occurs with pancuronium, are both surprising. Metronidazole has been reported to facilitate neuromuscular transmission and partially antagonize tubocurarine-induced neuromuscular blockade in isolated rat diaphragm (Jadhav et al., 1974), but in the concentrations and at the time of administration in this study, metronidazole did not exert any antagonistic effect to Org NC45. The fact that the potentiating action of metronidazole seen with Org NC45 was not reproducible when the closely related neuromuscular blocking drug pancuronium was used, suggests that it was not an effect of metronidazole on neuromuscular transmission. Rather, it may be secondary to an effect of metronidazole specifically on the distribution or metabolism of Org NC45. The slow onset of action of metronidazole in this respect may indicate that the effect is brought about by a metabolite rather than by metronidazole itself. The clinical implications of this observation are not yet clear, but caution may be necessary when Org NC45 is administered to patients treated with metronidazole, until the extent of the interaction in man, if any, is fully examined.

In summary, the results have demonstrated that Org NC45 resembles other non-depolarizing blocking drugs in that it is potentiated by halothane, enflurane, methoxyflurane, propanidid, sodium oxybate, Althesin and streptomycin to an important extent. Ketamine and thiopentone have a similar but weaker effect in therapeutic doses, whereas etomidate and methohexitone are effective only in doses that substantially exceed those used clinically. Where the same drugs were investigated, the results essentially agree with those of Krieg and others (1980) who used a different method of study. In addition, an apparently specific potentiating interaction between metronidazole and Org NC45 was demonstrated.

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INTERACTIONS ENTRE L'AGENT DE BLOCAGE NEUROMUSCULAIRE ORG NC45 ET CERTAINS AGENTS ANESTHESIANTS, ANALGESIQUES ET ANTIMICROBIENS

RESUME

On a étudié les effets qu'ont certains produits anesthésiants; ainsi que d'autres agents utilisés dans la pratique courante de l'anesthésie sur l'activité de blocage neuromusculaire de doses cumulées d'Org NC45, en utilisant des chats anesthésiés à l'aide de chloralose. Comme l'on pouvait s'y attendre d'après les recherches faites avec d'autres agents de blocage neuromusculaires, les agents anesthésiants administrés par voie intraveineuse et par inhalation ont permis de réduire les doses d'Org NC45 requises pour obtenir le blocage neuromusculaire. On a observé une interaction spécifique apparente de potentialisation entre l'Org NC45 et le métronidazole.

WECHSELWIRKUNGEN ZWISCHEN DER NEUROMUSKULAREN BLOCKIERUNGSDROGE ORD NC45 UND EINIGEN NARKOSE-, ANALGESIE- UND ANTIMIKROBISCHEN MITTELN

ZUSAMMENFASSUNG

Die Wirkungen einiger narkotischer und anderer Mittel der Narkosepraxis auf die neuromuskuläre Blockierungsaktivität kumulativer Dosen von Org NC45 wurde an mit Choloralose betäubten Katzen studiert. Wie nach Studien mit anderen neuromuskulären Blockierungsdrogen erwartet, wurden die für neuromuskuläre Blockierung benötigten Dosen von Org NC45 sowohl durch inhalierte als auch durch intravenös gegebene Narkosemittel reduziert. Eine offenbar speziell verstärkende Wechselwirkung zwischen Org NC45 und Metronidazol wurde beobachtet.

INTERACCION ENTRE LA DROGA DE BLOQUE NEUROMUSCULAR, ORG NC45, Y CIERTOS AGENTES ANESTESICOS, ANALGESICOS Y ANTIMICROBIALES

SUMARIO

Se han estudiado, en gatos anestesiados con cloralosa, los efectos de ciertos agentes anestésicos y de otro tipo agentes usados en la práctica anestésica con relación a la actividad de bloqueo neuromuscular de cantidades acumulativas de Org NC45. Como ya se esperaba a causa de los estudios efectuados con otras drogas de bloqueo neuromuscular, tanto los anestésicos de inhalación como los administración intravenosa reducieron las dosis de Org NC45 necesarias para el bloqueo neuromuscular. Se observó una interacción especifica, aparentemente potenciante, entre la Org NC45 y la metronidazola.

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EFFECTS OF CYANIDE ANTIDOTES USED WITH SODIUM NITROPRUSSIDE INFUSIONS: SODIUM THIOSULPHATE AND HYDROXOCOBALAMIN GIVEN PROPHYLACTICALLY TO DOGS

J. R. KRAPEZ, C. J. VESEY, L. ADAMS AND P. V. COLE

SUMMARY

Cyanide antidotes were given to dogs before an infusion of sodium nitroprusside 1.5 mg kg^{-1} for 1 h. Dogs given thiosulphate 75 mg kg^{-1} had significantly lower plasma and red cell cyanide concentrations while plasma thiocyanate concentrations were significantly increased in comparison with control. These changes were associated with only minimal disturbance of tissue oxygenation. There was no effect on red cell cyanide or thiocyanate concentrations in dogs treated with hydroxocobalamin 1.5 mg kg^{-1}, but plasma cyanide concentrations were significantly greater than in those receiving no antidote although there was less evidence of impaired oxygenation. There was no evidence of a synergistic action between thiosulphate and hydroxocobalamin. The vascular response to nitroprusside was unchanged in the thiosulphate-treated dogs, but was significantly greater in those given hydroxocobalamin. The implications for prophylaxis and treatment of cyanide poisoning following nitroprusside overdose are discussed.

Sodium nitroprusside ($Na_2Fe(CN)_5NO.2H_2O$), a powerful hypotensive agent, has proved useful in the production of controlled hypotension, and the acute management of hypertensive crises and cardiac failure (Cole, 1979). Its mechanism of action probably depends on the "FeNO" group (Johnson, 1929; Page et al., 1955), but during its subsequent breakdown significant quantities of cyanide appear in the blood (Vesey, Cole and Simpson, 1976). Overdosage with nitroprusside has, on a few occasions, resulted in cyanide poisoning and death (Jack, 1974; Merrifield and Blundell, 1974; Davies, Kadar et al., 1975) and several authors have proposed maximum total doses for short-term infusions (Davies, Greiss et al., 1975; Vesey, Cole and Simpson, 1976; Aitken et al., 1977; Michenfelder, 1977). Even when these recommended doses have not been exceeded the cyanide produced has been reported to affect tissue oxygenation both in animals (Michenfelder, 1977; Simpson et al., 1979) and man (Aitken et al., 1977). Any further decrease in the recommended safe dose of nitroprusside would reduce such effects but would limit the applicability of this useful drug. An alternative approach would be to "neutralize" the cyanide as it is formed.

Established antidotes to cyanide are amyl and sodium nitrites (Chen and Rose, 1952), cobalt edetate (Hillman, Bardhan and Bain, 1974), and sodium thiosulphate (Chen and Rose, 1952). Hydroxocobalamin (OHB_{12}) has been used on rare occasions (Lutier, Dusoleil and de Montgros, 1972). However, both nitrites and cobalt edetate have toxic side-effects (McKiernan, 1980) which severly limit the total dose. Sodium thiosulphate has no such effects and is the main source of sulphur for rhodanase, an enzyme which converts the trace amounts of cyanide arising during normal metabolism into thiocyanate. On the other hand, OHB_{12} combines directly with cyanide to form the innocuous compound, cyanocobalamin (Winter and Mushett, 1950; Mushett et al., 1952). Unfortunately, its high molecular weight necessitates impractically large doses if it is to be used as the sole antidote. However, in smaller amounts, it may enhance the action of thiosulphate (Evans, 1964; Delga, 1965; Tinker and Michenfelder, 1976). We have examined its action in less than the stoichiometric amount.

METHODS

Five groups of mongrel dogs were studied (table I). The group not receiving antidotes (group 1) formed part of an earlier series of experiments, the

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TABLE I. *Details of groups of dogs used. †Sodium nitroprusside (Analar) total dose dissolved in physiological saline 60 ml and administered during 1 h. *Antidotes to cyanide given as i.v. bolus doses: S = sodium thiosulphate* ($Na_2S_2O_3 5H_2O$) *75 mg kg*$^{-1}$ *(0.3 mmol kg*$^{-1}$*) in 5 ml of water 5 min before start of infusion;* OHB_{12} *= hydroxocobalamin (Aquacobalamin chloride, Glaxo Laboratories Ltd) 1.5 mg kg*$^{-1}$ *(approx. 1 µmol kg*$^{-1}$*) in 0.9% saline 5 ml given 4 min before the start of infusion;* $S+OHB_{12}$ *= both of the antidotes given at the above times before infusion;* $SmOHB_{12}$ *the antidote solutions mixed 10 min and administered 5 min before infusion*

	Group				
	1	2	3	4	5
n	8	6	8	6	6
Mean weight ± SEM (kg)	20.65 ± 2.08	21.40 ± 1.38	21.99 ± 1.01	24.27 ± 2.10	23.10 ± 1.76
SNP dose ± SEM (µmol kg^{-1})†	5.10 ± 0.23	5.31 ± 0.22	4.96 ± 0.02	5.05 ± 0.14	4.98 ± 0.15
Antidote administered*	—	S	OHB_{12}	$S+OHB_{12}$	$SmOHB_{12}$

results of which have been presented (Vesey et al., 1979). The remaining groups received randomly the antidotes indicated in table I. An identical anaesthetic technique was used in all groups. Anaesthesia was induced with pentobarbitone 35 mg kg^{-1} i.v., the trachea was intubated and the lungs ventilated with 60% nitrous oxide in oxygen. Arterial $P\text{CO}_2$ was maintained between 4.5 and 5.5 kPa. Additional doses of pentobarbitone were given as required, but care was taken not to administer increments during the infusion of SNP or immediately before making measurements. The superficial femoral artery was cannulated to permit monitoring of arterial pressure and sampling of arterial blood. A Swan–Ganz catheter was positioned in the pulmonary artery via the internal jugular vein. Nitroprusside was infused through a femoral vein catheter while the pulmonary artery lumen of the Swan–Ganz catheter was used for pressure monitoring, sampling of mixed venous blood and the administration of antidotes. Prior calibration of the thermistor of the Swan–Ganz catheter enabled temperature recordings to be made, heat loss being minimized by the use of a warming mattress. A catheter was inserted to the superior vena cava to permit injection of dye (indocyanine green) for determination of cardiac output.

The preparation was allowed to stabilize, systemic and pulmonary artery pressures were recorded and cardiac output was determined 20 min before commencing the infusion of nitroprusside. Samples were taken from the arterial catheter and analysed for plasma and red cell cyanide, plasma thiocyanate and blood lactate concentrations, blood-gas tensions and acid–base concentrations and oxygen content; oxygen content was also determined on a sample of mixed venous blood taken simultaneously. This sequence was repeated 10 min before the infusion of nitroprusside—which was of 1 h duration—and subsequently at 15, 30, 45, 60, 70, 90, 120 and 180 min after commencement of the infusion.

Cyanide was separately extracted from both plasma and washed red cells using the Boxer and Rickards (1951) aeration technique as described elsewhere (Vesey, Cole and Simpson, 1976; Vesey and Wilson, 1978). Red cell and plasma cyanide concentrations were separately determined because of the artefactual formation of cyanide in whole blood on assay (Vesey and Wilson, 1978), and because of the possible differences in the effects of the two antidotes on the distribution of cyanide between these two compartments. The plasma from OHB_{12}-treated dogs was protected from light during aeration. Cyanide and thiocyanate concentrations were determined by means of an autoanalytical technique which was a modified version of published methods (Casapieri, Scott and Simpson, 1970; Ellerker and Collinson, 1971). Blood lactate concentration was determined enzymatically (Boehringer). Blood-gas tensions and acid–base balance were measured using an IL 413 Blood Gas Analyser and oxygen content was estimated with a Lex-O_2-Con oxygen content analyser (Lexington Instruments Inc.). Cardiac output was estimated using a densitometer cuvette (XC 302, Waters Co. Minnesota) coupled to an XP densitometer and a chart recorder. Oxygen consumption was calculated from the cardiac output and the arterio–venous oxygen content difference using the Fick principle.

Eight dogs (group 1) were studied in the above fashion with no attempt being made to limit the increase in cyanide concentration (Vesey et al., 1979). The remaining dogs, in a random order, each received a bolus dose of one or other of the antidotes or a combination of both before the infusion (table I). The doses of thiosulphate ($Na_2S_2O_3.5H_2O$) and hydroxocobalamin were 75 mg kg^{-1} and 1.5 mg kg^{-1} respectively, these being 5 × and 0.04 × the stoichiometric amounts required for "neutralizing" the cyanide released.

The analysis technique used in this study for the determination of cyanide and thiocyanate concentrations has not previously been validated in the presence of thiosulphate. Such an assessment was considered desirable since both *in vitro* formation of thiocyanate from thiosulphate and cyanide on acidification and interference by decomposition products of thiosulphate (sulphur dioxide and hydrogen sulphide) with the colorimetric reaction could possibly occur. An identical preparation to that of the group 2 animals (thiosulphate only) was used, but no nitroprusside was administered to the dog. Instead, immediately following sampling at each of the times indicated in table II, blood from the dog was divided into two 10-ml aliquots and mixed with saline solutions of potassium cyanide of known concentration (to give blood concentrations of about 5 and 50 μmol litre^{-1}). Plasma and red cells were separated after 5 min incubation at room temperature and their cyanide content determined by our standard procedure. The amounts of cyanide recovered were expressed as a percentage of the cyanide added (table II). Thiocyanate measurements were also carried out on each sample of aerated plasma.

TABLE II. *Recovery of cyanide added to whole blood obtained from a dog at various times before and following a bolus dose of sodium thiosulphate 75 mg kg^{-1}. * 0.5 ml of a saline solution of KCn of measured concentration was added to 10-ml blood samples to give cyanide concentrations of (a) 5.15 and (b) 490 μmol litre^{-1}*

	Percentage recovery	
Sample times (min)	a*	b*
Before thiosulphate		
20	81.8	79.5
10	75.4	78.9
After thiosulphate		
15	76.2	77.3
30	78.2	79.1
60	71.5	75.8
90	79.6	77.0
180	78.0	77.0

RESULTS

The results of the cyanide recovery experiment (table II) show that thiosulphate, under the conditions of this study, did not interfere with the assay. Similarly, there was no significant effect on the low plasma thiocyanate concentrations of this dog (before thiosulphate: $\bar{x} = 6.85 \pm 0.21$ μmol litre^{-1}, $n = 4$; and after thiosulphate: $\bar{x} = 7.27 \pm 0.37$ μmol litre^{-1}, $n = 10$; $t = 0.68$, $P > 0.1$).

Systolic arterial pressures, expressed as a percentage of base line values, are given in table III and are shown for groups 1, 2 and 3 in figure 1. The hypotensive effect of the nitroprusside in all of the dogs which received thiosulphate was not significantly different from group 1. However, group 3 (OHB_{12} alone) showed a number of differences. An analysis of covariance which allowed for the variation in baseline pressures between individual dogs indicated that those dogs which received OHB_{12} (group 3) had a significantly lower systolic pressure for the duration of the infusion with nitroprusside than did the other groups of dogs ($P < 0.01$). The return to normotension following the end of infusion was more abrupt in groups 2, 4 and 5 (those which received thiosulphate) compared with group 1, and slower in group 3. The rates of recovery of arterial pressure over the periods 60–70 and 70–90 min are shown in table IV.

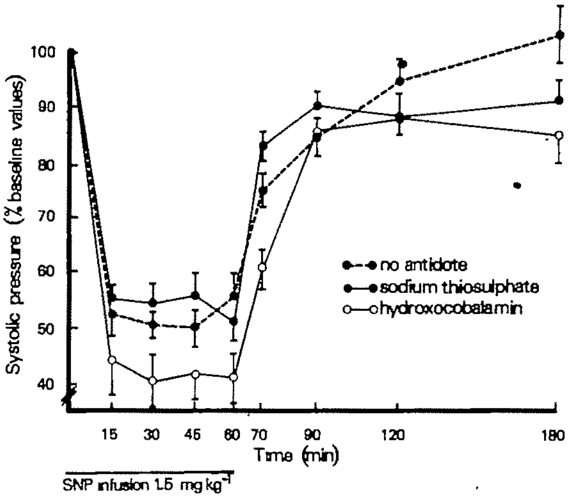

FIG. 1. Changes in systolic arterial pressure expressed as percentage of baseline values (mean ± SEM) during, and following, infusion of sodium nitroprusside 1.5 mg kg^{-1} in dogs given hydroxocobalamin, sodium thiosulphate, or no cyanide antidote, immediately before the infusion of SNP.

TABLE III. *Systolic arterial pressure (mm Hg) expressed as a percentage of baseline. Values significantly different from the corresponding values of group 1 indicated by:* **P < *0.01*, *P < *0.05. Group 3 values significantly smaller than corresponding group 2 values indicated by:* ***P < *0.001*, ‡P < *0.05. Values at time zero are absolute pressures*

Time (min)	Group 1 (*n* = 8)		Group 2 (*n* = 6)		Group 3 (*n* = 7)		Group 4 (*n* = 6)		Group 5 (*n* = 6)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
0	182.5	10.4	173.2	7.8	188.8	8.7	183.8	14.7	172.1	10.1
15	52.6	4.3	55.4	2.9	44.8	6.5	53.0	7.0	46.6	4.1
30	50.5	2.5	54.6	3.9	40.2‡	5.1	54.6	10.0	50.0	4.2
45	51.3	2.4	56.4	4.3	40.5‡	4.7	53.4	7.4	49.6	4.5
60	55.8	4.1	51.8	3.7	40.8*	4.5	57.1	7.7	54.8	5.1
70	75.2	3.2	83.5	3.2	60.6** ***	3.4	87.2	11.4	87.6	7.0
90	86.0	4.3	91.7	2.3	86.1	2.7	95.8	8.0	100.7	7.0
120	94.8	4.6	90.8	3.2	88.8	2.7	92.8	2.4	100.6	7.5
180	103.4	5.8	92.9	4.3	86.7	5.3	80.6	6.7	90.8	8.5

TABLE IV. *Changes in systolic arterial pressure (SAP) (expressed as differences in percentage of baseline values) over the first 10-min and the subsequent 20-min intervals immediately following infusion. Values significantly different from group 1 values indicated by:* ***P < *0.001;* **P < *0.01;* *P < *0.05. Statistically significant differences between group 3 and other groups shown as:* ††P < *0.01*, ‡P < *0.05. Values given in this table were obtained from the data in table III by subtraction of the 60- and 70-min values from the 70- and 90-min values respectively*

Time period (min)	Group 1 (*n* = 8)		Group 2 (*n* = 6)		Group 3 (*n* = 7)		Group 4 (*n* = 6)		Group 5 (*n* = 6)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
SAP (mm Hg) at 60 min (end of SNP infusion)	100	5.5	89.5	7.5	78.6	9.5	100	8.2	91.7	4.8
60–70 (first 10 min of recovery from hypotension)	19.4	2.1	31.7**‡	3.3	19.9	2.8	30.1*	5.0	32.9**††	2.6
70–90 (subsequent 20 min)	10.8	1.8	8.2††	2.8	25.5***	3.0	8.6††	3.6	13.0‡	2.6

The increases in plasma cyanide concentration (mean ± SEM) are presented in table V. The values obtained for the groups receiving thiosulphate were significantly less than in group 1 (15–70 min samples in groups 2 and 4; 45–70 min samples in group 5). However, where OHB_{12} was used alone (group 3) plasma cyanide concentrations were significantly *greater* than in those receiving no antidote (group 1) for the 45–120 min period. (The maximum mean concentration was more than 2.5 times the corresponding group 1 value.)

Increases in red cell cyanide concentration are recorded in table VI (mean ± SEM) and are much smaller in all three groups receiving thiosulphate than in group 1 at all sampling times during and after the infusion. The red cell cyanide concentrations in group 3 (OHB_{12} alone) were not significantly different from those of group 1.

The increases in mean plasma thiocyanate concentration (table VII) in the groups receiving thiosulphate (2, 4 and 5) were significantly greater than those of group 1. In group 3, however, the increases in plasma thiocyanate concentration were not significantly different from the latter. Where OHB_{12} was used in conjunction with thiosulphate (groups 4 and 5) the increase in thiocyanate concentration was not as large as in group 2, although the differences were not significant at the 5% level.

The time course of the changes in plasma cyanide, red cell cyanide and plasma thiocyanate concentrations for group 1, 2 and 3 animals are compared in figure 2.

An increase in blood lactate concentration occurred during the infusion in all of the group 1 dogs. In contrast, all of the antidote-treated groups had significantly smaller mean blood

TABLE V. *Mean increases in plasma cyanide concentrations* (μmol litre^{-1}) *in dogs receiving antidotes compared with those dogs not receiving antidote. Increases significantly different from those of group 1 indicated by:* ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. ¶*Apart from this value* ($P < 0.05$) *differences between group 4 and 5 are not significant. The differences between group 2 and group 3 are significant at* ††$P < 0.01$ *and* ‡$P < 0.05$. §*Number of measurements at these times* = n − 1. *Values at time zero are absolute concentrations*

Sample time (min)	Group 1 (*n* = 8)		Group 2 (*n* = 6)		Group 3 (*n* = 8)		Group 4 (*n* = 6)		Group 5 (*n* = 6)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
0	0.18	0.05	0.06	0.01	0.18	0.07	0.15	0.08	0.19	0.16
15	0.67	0.06	0.31*	0.04	0.71‡§	0.13	0.26**	0.07	0.54¶	0.09
30	1.09	0.06	0.28***	0.03	1.82†	0.39	0.29***	0.12	0.78§	0.28
45	1.41	0.15	0.29***	0.04	3.13*††	0.74	0.36***	0.11	0.56**	0.12
60	1.37	0.17	0.28***	0.06	3.7*††	0.88	0.40**	0.16	0.38**	0.13
70	1.02§	0.19	0.22**	0.05	3.13*††	0.79	0.17**	0.09	0.25**	0.15
90	0.48	0.13	0.17§	0.08	2.25*‡	0.61	0.18	0.07	0.22	0.07
120	0.15§	0.11	0.14	0.08	1.52*	0.55	0.05	0.12	0.20	0.09
180	−0.03	0.07	0.13	0.13	0.14	0.11	0.11	0.13	0.06	0.05

TABLE VI. *Mean increases in red cell cyanide concentrations* (μmol/litre *packed cells*) *in dogs receiving antidotes compared with those dogs not receiving antidote. Increases significantly different from those of group 1 indicated by:* ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. *Values of group 3 are not significantly different from group 1 values, but the differences from group 2 are highly significant:* †$P < 0.001$, ‡$P < 0.02$. *There are no significant differences between groups 2, 4 and 5.* §*Number of measurements at these times* = n − 1. *Values at time zero are absolute concentrations*

Sample time (min)	Group 1 (*n* = 8)		Group 2 (*n* = 6)		Group 3 (*n* = 8)		Group 4 (*n* = 6)		Group 5 (*n* = 6)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
0	0.79	0.12	0.64	0.15	1.02	0.19	0.54	0.12	0.58	0.09
15	38.6	2.5	6.8***	0.9	31.8†	2.6	8.4***	0.9	7.5***	1.1
30	70.0	5.2	8.8***	0.9	60.4†	4.9	11.1***	1.1	11.3***	1.2
45	97.9	6.9	11.3***	1.0	89.4†	7.1	13.3***	1.3	13.9***	1.7
60	118.2	8.4	10.8***	1.0	117.8†	8.0	13.6***	1.8	13.8***	1.8
70	109.7	9.5	5.4***	0.7	106.4†	8.6	6.8***	1.1	6.8***	0.9
90	80.2	11.9	1.9***	0.3	72.6†§	8.4	2.8***§	0.5	3.0***	0.8
120	43.2	11.2	0.8**	0.1	43.3†	9.6	1.0**	0.2	1.1**	0.5
180	8.5	3.0	0.4*	0.2	6.5‡	1.9	0.6*	0.1	0.6*	0.2

TABLE VII. *Mean increases in plasma thiocyanate concentrations* (μmol litre^{-1}) *in dogs receiving antidotes compared with dogs not receiving antidote. Increases significantly greater than group 1 values indicated by:* ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. *Significant increases in thiocyanate concentrations in groups 2, 4 and 5 compared with those of group 3 are shown by:* †$P < 0.001$; ††$P < 0.01$; ‡$P < 0.05$. §*Number of measurements obtained at this time* = n − 1. *Values at time zero are absolute concentrations*

Sample time (min)	Group 1 (*n* = 8)		Group 2 (*n* = 6)		Group 3 (*n* = 8)		Group 4 (*n* = 6)		Group 5 (*n* = 6)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
0	11.1	3.1	14.8	2.6	20.5	3.6	16.0§	3.1	15.0	2.7
15	7.8	1.9	23.3***†	1.2	9.4	1.9	23.2***††	2.9	17.5**‡	2.5
30	16.5	2.8	45.1***†	3.7	17.1	2.5	39.5***†	2.7	39.2***†	4.3
45	22.8	2.9	66.9***†	5.1	23.8	3.2	61.5***†	6.0	54.0***†	4.6
60	28.4	3.8	80.8***†	6.6	29.5	3.2	74.8***†	7.0	69.2***†	5.5
70	32.5	4.4	80.8***†	6.7	33.1	4.1	74.0***†	7.8	74.5***†	7.3
90	39.5	4.5	75.6***††	6.7	41.0	5.1	72.8**††	7.7	63.0**††	5.6
120	45.6	4.0	73.1**‡	5.9	50.9	5.5	70.3**‡	7.1	59.5*	5.5
180	51.3	3.8	71.9**	5.3	60.8	5.0	66.0	8.2	57.0	6.2

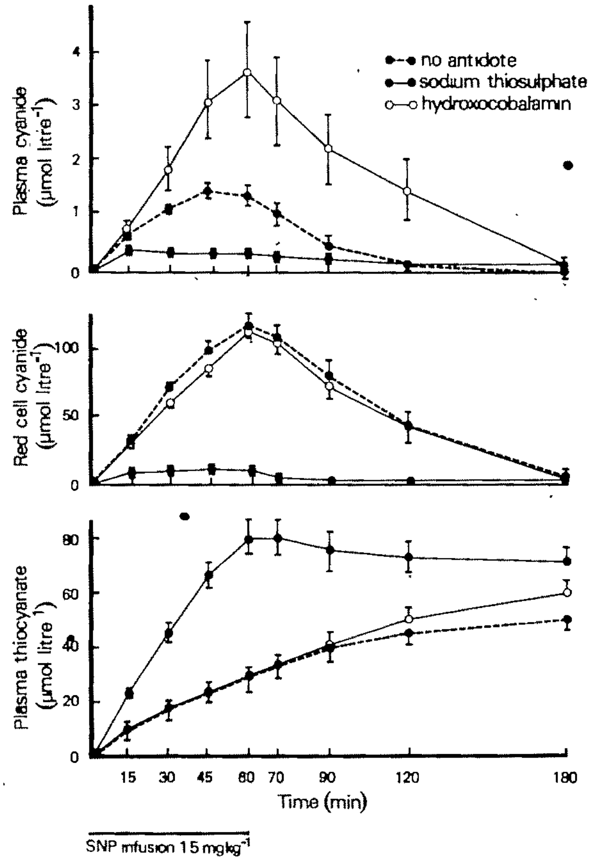

FIG. 2. Blood concentrations of cyanide and thiocyanate (mean ± SEM) during, and subsequent to, an infusion of sodium nitroprusside 1.5 mg kg^{-1} in dogs given hydroxocobalamin, sodium thiosulphate, or no antidote before infusion.

lactate concentrations (table VIII) over the period of 15–90 min. The values in all of the groups receiving OHB_{12} were consistently greater than the one receiving thiosulphate alone, although the differences were not statistically significant.

Oxygen consumption values (expressed as a mean percentage of baseline values, ± SEM) were only obtained for groups 1, 2, 4 and 5 (table IX). Oxygen consumption decreased to 87% of baseline in the animals receiving no antidote whereas values in the other groups exceeded 100%. However, wide variation resulted in a statistically significant difference from group 1 on four occasions only in group 2 (15, 30, 45 and 60 min) and twice in group 5 (30–60 min).

Although base deficit increased only slightly in the dogs in group 2 (thiosulphate only: table X) the values were significantly different from group 1 at 70 min only. Base deficit values in the remaining groups were not significantly different from group 1 at any time despite the significantly smaller lactate concentrations.

Changes in blood lactate concentration, base deficit and oxygen consumption in groups 1, 2 and 3 are compared in figure 3.

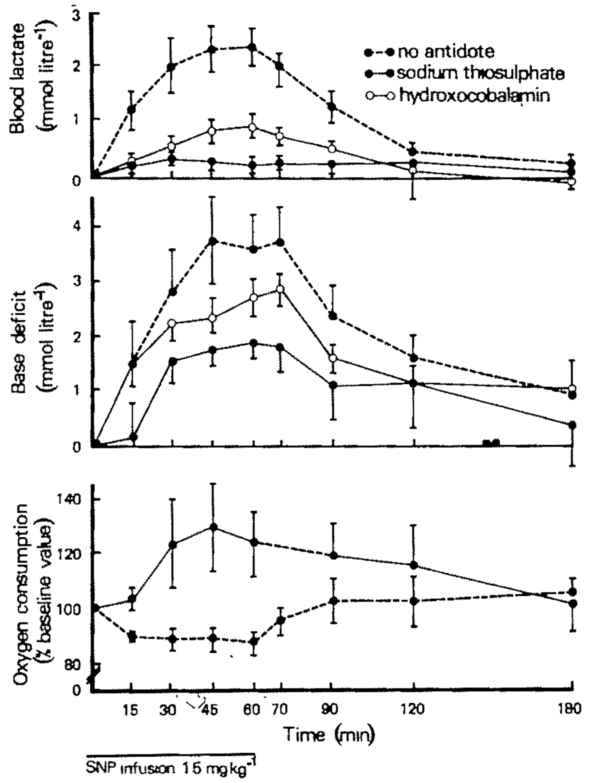

FIG. 3. Blood lactate concentration, base deficit and oxygen consumption (mean ± SEM) during, and for 2 h after, a 1-h infusion of sodium nitroprusside 1.5 mg kg^{-1} in dogs given a bolus dose of a cyanide antidote just before the start of the SNP infusion, compared with those given no antidote.

DISCUSSION

The standard treatment for cyanide poisoning includes the administration of amyl nitrite, sodium nitrite and sodium thiosulphate (Chen, Rose and Clowes, 1933; Chen and Rose, 1952). The nitrites are used to augment the antidotal effect of thiosulphate (Frankenberg and Sorbo, 1973) because it is considered to have a slow onset of action (Evans, 1964; Friedberg, 1968). They rapidly convert haemoglobin to methaemoglobin, which has a greater affinity for cyanide than does cytochrome oxidase (Schubert and Brill, 1969).

TABLE VIII. *Mean increases in blood lactate concentrations (mmol* litre^{-1}*) in dogs receiving cyanide antidotes compared with dogs not receiving antidote. Increases which are significantly smaller than in group 1 indicated by:* ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$. §*Numbers of values obtained at these times* = n − *1. Values at time zero are absolute concentrations*

Sample time (min)	Group 1 ($n = 8$)		Group 2 ($n = 6$)		Group 3 ($n = 8$)		Group 4 ($n = 6$)		Group 5 ($n = 6$)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
0	1.63	0.41	0.93	0.13	1.33	0.15	1.05	0.21	1.82	0.60
15	1.22	0.31	0.19*	0.13	0.25*	0.12	0.43	0.20	0.26*	0.14
30	2.02	0.49	0.38*	0.20	0.59*	0.15	0.63*	0.29	0.38*	0.19
45	2.37	0.42	0.24*	0.16	0.84**	0.18	0.72*	0.34	0.47**	0.20
60	2.38	0.34	0.19***	0.16	0.94**	0.18	0.78**	0.39	0.40***	0.17
70	2.01	0.32	0.25***	0.12	0.75**	0.16	0.82*	0.46	0.31**	0.27
90	1.33	0.26	0.26**	0.22	0.54*	0.13	0.53	0.29	0.30**	0.18
120	0.48§	0.18	0.26	0.29	0.18§	0.22	0.57	0.25	−0.63	0.72
180	0.29	0.18	0.11	0.26	−0.06	0.11	0.40	0.23	−0.31	0.86

TABLE IX. *Mean changes in oxygen consumption (% baseline) in dogs receiving antidotes compared with those not receiving antidote. Values at time zero are absolute values (ml* min^{-1}*). No measurements were made in group 3. Values showing significant differences from those of group 1 shown by:* **$P < 0.02$, *$P < 0.05$. §n − *1 measurements obtained at these times.* §§n − *2 measurements obtained*

Sample time (min)	Group 1 ($n = 8$)		Group 2 ($n = 5$)		Group 3	Group 4 ($n = 5$)		Group 5 ($n = 5$)	
	Mean	SEM	Mean	SEM		Mean	SEM	Mean	SEM
0	131.5	17.2	116.02	8.4	—	151.1	28.3	128.7	10.9
15	89§	2.1	103**	4.1	—	102	9.0	101	6.3
30	88§	3.7	124*§	16.3	—	106	12.9	101*	2.9
45	89	5.3	130**§	15.9	—	104	9.5	99	8.0
60	87§	4.2	124**§	11.6	—	109	13.3	117**	8.9
70	95	4.8	109§§	3.8	—	104	6.9	100	9.5
90	102	8.3	119	11.7	—	122	12.7	102	7.6
120	102	8.6	115	14.7	—	110	19.5	104	9.7
180	105	5.6	101	10.0	—	117	31.8	110	8.5

TABLE X. *Mean change in base deficit (mmol* litre^{-1}*) in dogs receiving cyanide antidotes compared with those not receiving antidote. Only value significantly different from group 1 shown by:* *$P < 0.05$. §*Number of values obtained at these times* = n − *1. Values at time zero are absolute values*

Sample time (min)	Group 1 ($n = 8$)		Group 2 ($n = 6$)		Group 3 ($n = 8$)		Group 4 ($n = 6$)		Group 5 ($n = 6$)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
0	0.5	1.09	3.4	0.33	4.2	0.56	3.9	0.95	3.0	0.93
15	1.5	0.78	0.12	0.61	1.5	0.42	1.92	0.84	2.12	0.61
30	2.8	0.84	1.6	0.47	2.3	0.39	1.97	0.48	3.10	0.85
45	3.8	0.80	1.8	0.32	2.4	0.33	2.33	0.77	3.10	0.85
60	3.6	0.68	1.9	0.30	2.7	0.32	2.58	0.78	2.83	0.43
70	3.8	0.65	1.8*§	0.43	2.9	0.34	2.57	0.86	2.83	0.48
90	2.4	0.56	1.1	0.62	1.6	0.27	2.38§	0.69	2.08	0.40
120	1.6	0.48	1.2§	0.82	1.2	0.29	2.02	0.72	1.23	0.49
180	0.94	1.07	0.42	0.73	1.1	0.51	2.20	0.91	1.40*	0.45

Thiosulphate then provides sulphur for the conversion of this "sequestered" cyanide to thiocyanate by the mitochondrial enzyme rhodanase (thiosulphate sulphurtransferase, E.C.2,8,1,1). Thus, the combination of nitrite and thiosulphate has been recommended for the management of cyanide intoxication resulting from the infusion of sodium nitroprusside (Davies, Kadar et al., 1975; Cohn and Burke, 1979).

This study has demonstrated that thiosulphate acts more rapidly than has been thought. The maintenance of low blood cyanide concentrations coupled with the rapid increase in plasma thiocyanate concentrations and unimpaired tissue oxygenation in those animals which received thiosulphate (figs 2, 3) strongly suggests that cyanide was converted to thiocyanate as quickly as it was released from the nitroprusside. Schubert and Brill (1969) consider thiosulphate to act rapidly, while other workers (Friedberg and Shukla, 1975; Frankenberg and Sorbo, 1973) have demonstrated its long duration of action. In view of these findings we believe that nitrites are, at best, unnecessary in the treatment of sodium nitroprusside overdose. Indeed, there are good reasons for not giving nitrites. They have a marked hypotensive action when used to produce the recommended 30% methaemoglobinaemia (Kiese and Weger, 1969). Toxic effects appear at 40% methaemoglobinaemia and such toxicity has occurred in the treatment of cyanide poisoning (Berlin, 1970; Douze and van Heijst, 1973), and Hillman, Bardhan and Bain (1974) have questioned their value for this purpose. Thiosulphate alone or in combination with cobalt edetate would seem to offer an effective alternative.

Unlike thiosulphate, hydroxocobalamin (OHB_{12}) has only rarely been used as an antidote in cyanide poisoning, when it has been given in massive doses (Lutier, Dusoleil and De Montgros, 1972). Its efficacy, when used in large amounts, has also been demonstrated in animals receiving infusions of nitroprusside (Posner, Rodkey and Tobey, 1976; Posner, Tobey and McElroy, 1976). However, evidence exists for both an involvement of OHB_{12} at physiological concentrations in normal cyanide metabolism (Boxer and Rickards, 1952; Foulds and Pettigrew, 1977) and also for a significant antidotal effect at low doses (Vesey et al., 1974). These factors, and the impractical size of a full "neutralizing" dose, prompted our use of OHB_{12} only 1.5 $mg\,kg^{-1}$ (to "neutralize" completely the cyanide released from SNP 100 mg would require OHB_{12} 2.5 g). Given alone at this dose (molar ratio OHB_{12}: HCn = 1:25) it had no effect on red cell cyanide or plasma thiocyanate concentrations. However, plasma cyanide concentrations were significantly greater than in the animals receiving no antidote, whilst blood lactate concentrations were significantly less. These paradoxical results could be explained if the "extra" cyanide in the plasma was detectable by the assay procedure, but was unable to exert a histotoxic effect. This is a distinct possibility, since the formation of dicyanocobalamin has been demonstrated *in vitro* (Beaven et al., 1950; Cooley et al., 1951; Conn, Norman and Wartman, 1951). Unlike cyanocobalamin, the dicyano compound is unstable at low pH (even in the absence of light) breaking down to yield cyanocobalamin and free cyanide. Thus, in our assay procedure in which plasma was acidified and the cyanide extracted in the absence of light, the cyanide from dicyanocobalamin would be set free and measured. Even so, it must be concluded that, at the doses used, OHB_{12} was a less effective antidote than thiosulphate. Encouraging results have been described in man by Cottrell and colleagues (1978), who found that OHB_{12} infused continuously at the same time as nitroprusside resulted in decreases in plasma and red cell cyanide concentrations. The total dose of OHB_{12} infused was similar to that used in this study, but analysis of cyanide concentrations was carried out using a cyanide-sensitive electrode. This technique has been shown to be subject to considerable error when used to determine cyanide concentrations in body fluids (Kistner et al., 1979).

Synergism between OHB_{12} and thiosulphate as cyanide antagonists has been described for guinea-pigs (Delga, 1965) and for mice (Evans, 1964; Friedberg and Shukla, 1975). In this study, although there were no statistically significant differences between any of the thiosulphate treated groups (groups 2, 4 and 5), those that also received OHB_{12} tended to have greater plasma cyanide and blood lactate concentrations and smaller plasma thiocyanate concentrations. Therefore, we must conclude that, under the conditions of this study, there was no synergism between the two antidotes. Our results tend to agree with the reported adverse interaction between OHB_{12} and thiosulphate (Evans, 1964; C. H. Dash, Glaxo Laboratories, personal communication).

Various authors have suggested that an increase in plasma cyanide concentration produced during the infusion of nitroprusside may attenuate its hypotensive action either by circulatory stimulation (Posner, Rodkey and Tobey, 1976) or by blocking the response of vascular smooth muscle (Greiss, Tremblay and Davies, 1976). *In vitro* studies have indeed confirmed that cyanide can inhibit the action of nitroprusside (Tremblay et al., 1977; Grayling, Miller and Peach, 1978), although these results were obtained under conditions which are difficult to relate to clinical practice. In this study although blood cyanide concentrations were much greater in the animals receiving no antidote than in those treated with thiosulphate (group 2) there was no significant difference in the degree of hypotension. It is possible that thiosulphate may limit the action of nitroprusside either by increasing its rate of breakdown or by producing a more rapid regeneration of sulphydryl receptors in the vessel walls (Needleman, Jaschik and Johnson, 1973), since there was faster return to normal arterial pressure in the thiosulphate-treated animals (table IV). It is noticeable that this effect was not present in the animals given OHB_{12} alone, and that there was a greater decrease in arterial pressure in this group of animals. (The possibility that the increase in the hypotensive effect in the OHB_{12}-treated animals might be a result of dicyanocobalamin was investigated by administering a bolus injection of the compound (7.7 mg kg^{-1}) to one animal. There was no discernable effect on arterial pressure.)

The animals of group 1 were part of a previous study. It is recognized that this sequential rather than randomized order could be criticized, despite the fact that all the present authors were involved in both studies and only 10 months separated the two. Accordingly, one "no antidote" experiment was performed during the present series and the results were, in every way, typical of the previous study.

The large variation in oxygen consumption values makes it difficult to draw firm conclusions about differences between the groups studied. Apart from the known wide individual variation (63–184 ml min^{-1}) (Altman and Dittmer, 1971) oxygen consumption can be affected by a number of other factors, including anaesthesia and body temperature. Barbiturates, in particular, are known to depress oxygen consumption and, to avoid this source of error, pentobarbitone was not administered during the period of infusion. Decreases in body temperature result in changes in oxygen consumption and, therefore, variations in temperature were limited to ± 1 °C for each dog. Notwithstanding the potential sources of error, the fact that oxygen consumption decreased in six of eight dogs not given antidotes and increased in 10 of 14 dogs which did recieve antidotes, is noteworthy. When combined with observed differences in lactate concentration between "no antidote" and "antidote" animals, it is difficult not to conclude that tissue hypoxia occurs during an infusion of nitroprusside (even if the dose used is limited to 1.5 mg kg^{-1}), and that the increases in cyanide concentration are most likely to be responsible. The increase in oxygen consumption in the antidote-treated animals was probably a result of the hyperventilation which almost invariably accompanied the hypotension. We noted hyperventilation in dogs given nitroprusside or cyanide (Simpson et al., 1979) and attributed it to an increase in blood cyanide concentration. This would now seem to be an incomplete explanation, and it is probable that some other factor (for example the hypotension *per se*) is also responsible for the increase in respiratory activity.

The concentration of blood lactate and the base deficit are related indices of tissue oxygenation. Lactate concentrations were significantly smaller in the antidote groups; there was virtually no change from the pre-infusion value in the group receiving thiosulphate only. Base deficit values, on the other hand, were not significantly improved by the administration of antidotes (apart from group 2, 70-min sample). This is at variance with our previous findings (Simpson et al., 1979) when we concluded that base deficit values are closely related to lactate concentration and accordingly provide an indication of tissue hypoxia during the infusion of SNP. Factors other than tissue oxygenation must be involved in the generation of the base deficit in this present study.

We suggest that sodium thiosulphate, 75 mg kg^{-1} is an effective antidote, with negligible toxicity, for the prophylactic treatment of the increases in cyanide concentration produced by the infusion of nitroprusside. Hydroxocobalamin 1.5 mg kg^{-1} was much less effective at limiting the increases in cyanide concentration, but it did decrease the tendency to lactic acidosis. Higher dosage or continuous infusion of OHB_{12} may produce better results, and further investigation is required. Whether cyanide antagonists should be administered before all infusions of nitroprusside is debatable. This study suggests that there could be considerable advantage in giving thiosulphate when the anaesthetist anticipates using close to the maximum recommended dose (1.5 mg kg^{-1}) or where resistance or tachyphylaxis are likely. Given our current lack of knowledge of the effects of cyanide at less than lethal concentrations, it is impossible to make scientifically-based recommendations. It would seem sensible, however, to limit the concentrations of this poisonous substance, particularly when this can be done safely and effectively.

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EFFETS DES ANTIDOTES DU CYANURE UTILISES AVEC LES PERFUSIONS DE NITROPRUSSIATE DE SODIUM: THIOSULFATE DE SODIUM ET HYDROXOCOBALAMINE ADMINISTRES A TITRE PROPHYLACTIQUE A DES CHIENS

RESUME

On a administré à des chiens des antidotes du cyanure avant une perfusion de nitroprussiate de sodium 1,5 mg kg^{-1} d'une durée d'une heure. Les chiens auxquels on avait administré du thiosulfate 75 mg kg^{-1} ont eu des concentrations du cyanure dans les globules rouges et dans le plasma nettement plus faibles, alors que les concentrations de thiocyanate ont augmenté d'une manière significative par rapport aux témoins. Ces variations n'ont été associées qu'à des perturbations minimales dans l'oxygénation des tissues. Les concentrations de cyanure ou de thiocyanate dans les globules rouges n'ont pas été affectées lorsque les chiens avaient été traités à l'hydroxocobalamine 1,5 mg kg^{-1}, mais les concentrations de cyanure dans le plasma ont été nettement plus fortes que sur les animaux n'ayant reçu aucun antidote, bien qu'il ait été moins évident que l'oxygénation était altérée. Il n'y a eu aucune évidence d'une action synergique entre le thiosulfate et l'hydroxocobalamine. La réaction vasculaire au nitroprussiate est demeurée sans changement lorsque les chiens ont été traités au thiosulfate, mais elle a été nettement plus forte sur ceux auxquels on avait administré de l'hydroxocobalamine. Les implications pour la prophylaxie et le traitement des empoisonnements par le cyanure dus à un surdosage de nitroprussiate sont discutés dans cet article.

WIRKUNGEN VON ZYANID-GEGENMITTEL ZUSAMMEN MIT NATRIUMNITROPRUSSID-INFUSIONEN: NATRIUMTHIOSULFAT UND HYDROXOCOBALAMIN WURDE HUNDEN PROPHYLAKTISCH VERABREICHT

ZUSAMMENFASSUNG

Zyanid-Gegenmittel wurde Hunden vor einer Infusion von Natriumnitroprussid 1,5 mg kg^{-1} für eine Stunde verabreicht. Hunde, die Thiosulfat 75 mg kg^{-1} erhielten, zeighten beachtlich niedrigere Zyanidkonzentrationen in Plasma und roten Zellen, während die Plasmakonzentrationen von Thiocyanat im Vergleich zu den Kontrollwerten wesentlich erhöht waren. Diese Änderungen waren mit nur einer minimalen Störung der Gewebe-Sauerstoffanreicherung verbunden. Bei Hunden, die mit Hydroxocobalamin 1,5 mg kg^{-1} behandelt wurden, gab es keine Auswirkung auf das Zyanid in den roten Zellen oder auf Thiocyanat-Konzentrationen, aber die Plasma-Zyanidkonzentrationen waren wesentlich höher als bei den Hunden, die kein Gegenmittel erhielten, wenn es hier auch weniger Beweise für eine beeinträchtigte Sauerstoffanreicherung gab. Es gab keine Anzeichen einer synergistischen Aktivität zwischen Thiosulfat und Hydroxocobalamin. Die Gefässreaktion auf Nitroprussid war bei den mit Thiosulfat behandelten Hunden unverändert, war aber wesentlich stärker bei der Behandlung mit Hydroxocobalamin. Die Konsequenzen davon für Prophylaxe und Behandlung von Zyanidvergiftung nach einer Nitroprussid-Überdosis werden diskutiert.

EFECTOS DE LOS ANTIDOTOS DE CIANURO USADOS CON INFUSIONES DE NITROPRUSIATO SODICO: ADMINISTRACION PROFILACTICA DE TIOSULFATO Y DE HIDROXOCOBALAMINA A PERROS

SUMMARIO

Se sometieron perros a la acción antídotos de cianuro antes de una infusión de 1,5 mg kg^{-1} de nitroprusiato sódico por espacio de una hora. Los perros a los que se les administró 75 mg kg^{-1} de tiosulfato presentaron concentraciones significativamente inferiores de plasma y de celulas rojas de cianuro mientras que las concentraciones de tiocianato en el plasma aumentaron de

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forma significativa en comparación con los grupos de control. Estos cambios se asociaron con sólo mínimas perturbaciones en la oxigenación de los tejidos. No hubo efecto alguno en las concentraciones de células rojas de cianuro o de tiocianato en los perros tratados con 1,5 mg kg^{-1} de hidroxocobalamina, pero las concentraciones de cianuro en el plasma fueron significativamente superiores que las de aquellos a los que no se les adminstró antídoto, aunque hubo menos evidencia de dificultad en oxigenación. No se presentó evidencia alguna de actividad sinergística entre el tiosulfato y la hidroxocobalamina. Le respuesta vascular al nitroprusiato no varió en los perros tratados con tiosulfato, pero ésta fue significativamente mayor en los perros tratados con hidroxocobalamina. Se discuten las repercusiones relativas a la profilaxis y al tratamiento del envenamiento por cianuro a raís de una sobredosis de nitroprusiato.

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PHARMACOKINETICS AND ANALGESIC EFFECTS OF I.M. AND ORAL KETAMINE

I. S. GRANT, W. S. NIMMO AND J. A. CLEMENTS

SUMMARY

The pharmacokinetics and analgesic effects of i.m. and oral ketamine in a dose of $0.5\,mg\,kg^{-1}$ were determined in six healthy volunteers. Analgesia was measured by the submaximal effort tourniquet test. Following both routes of administration, ketamine prolonged the period of pain-free ischaemic exercise. Pain thresholds were increased at 15 min and 30 min after i.m. injection and at 30 min after oral ketamine. The plasma ketamine concentration associated with analgesia was $150\,ng\,ml^{-1}$ following the i.m. dose, but only $40\,ng\,ml^{-1}$ after the oral dose. Oral administration was, however, associated with much greater concentrations of the metabolite norketamine, which may have contributed to the analgesic effect.

Ketamine has analgesic properties when given in sub-anaesthetic doses (Bovill and Dundee, 1971; Caro, 1974; Wilson, Herrin and Richey, 1978) and has been used as repeat i.v. injections of $0.5\,mg\,kg^{-1}$ (Austin, 1976) or as an infusion of $1–2\,mg\,min^{-1}$ to provide analgesia after operation (Ito and Ichiyanagi, 1974; Clausen, Sinclair and Hasselt, 1975).

In healthy volunteers, i.v. ketamine in doses of $0.125\,mg\,kg^{-1}$ and $0.25\,mg\,kg^{-1}$ increased pain thresholds when the plasma ketamine concentration was greater than $100\,ng\,ml^{-1}$, but the duration of analgesia was very short (Clements and Nimmo, 1981). The pharmacokinetics of i.v. ketamine in those doses were similar to those of anaesthetic doses (Chang and Glazko, 1972; Wieber et al., 1975).

I.m. injection is recommended by the manufacturers for inducing anaesthesia, but there is little information on its i.m. use for analgesia, nor any pharmacokinetic data following i.m. injection. Similarly, there is little information about orally administered ketamine, although self administration of 300 mg has been reported to produce unconsciousness (Johnstone, 1972).

In the present study, we have investigated the pharmacokinetics and analgesic activity of i.m. and oral ketamine in a dose of $0.5\,mg\,kg^{-1}$.

SUBJECTS AND METHODS

Six fasting, healthy adult volunteers (age 31.8 ± (SEM) 2.0 yr; weight 70.7 ± 4.4 kg) were studied on three occasions at least 1 week apart: once after ketamine $0.5\,mg\,kg^{-1}$ orally, once after ketamine $0.5\,mg\,kg^{-1}$ i.m. and once after placebo. The order was randomized, and the subjects were unaware of the nature of the drug administered. On each occasion they received a drink of 50 ml of orange juice (with or without ketamine in solution) over 1 min and simultaneously an i.m. injection of saline or ketamine into the triceps of the dominant arm.

Blood samples were taken at intervals for 7 h from an indwelling venous cannula in the dominant arm. The plasma was separated and stored frozen until measurement of plasma ketamine and its metabolites.

Analgesia

Analgesia was measured by a submaximal effort tourniquet test similar to that of Harrison and Bigelow (1943), and described fully by Clements and Nimmo (1981). After application of a sphygmomanometer cuff (inflated to $250\,mm\,Hg^{-1}$) on the non-dominant arm, a spring-loaded "wrist exerciser" was squeezed once per second. A suitable workload was fixed for each subject by setting the compression distance. As before, pain scores (none = 0, mild = 1, moderate = 2, severe = 3 and intolerable = 4) were recorded at 15-s intervals. "Tourniquet time" was noted when the pain became intolerable and the cuff was immediately deflated. Subjects were

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tested 30 min and 15 min before drug administration, and at 15-min intervals for 2 h after administration.

Tests of statistical significance were carried out by paired *t* test.

Ketamine analysis

Plasma samples were analysed for ketamine, norketamine (metabolite I) and dehydronorketamine (metabolite II) as their heptafluorobutyryl derivatives on a gas–liquid chromatograph with electron-capture detection (Walle and Ehrsson, 1970; Chang and Glazko, 1972; Clements and Nimmo, 1981).

Pharmacokinetics

Plasma ketamine concentration-time points were fitted to a two-compartment open model by non-linear regression (Clements and Prescott, 1976) to give estimates of the absorption and disposition half-lives. Bioavailability was calculated from the ratio of the areas under the concentration time curve (with correction for area after the final point) following oral or i.m. administration to that following i.v. injection, with correction for the dose. Apparent absorption rate constants were not corrected for incomplete bioavailability (Gibaldi and Perrier, 1975).

RESULTS

All subjects remained conscious and orientated after ketamine 0.5 mg kg^{-1}. Some lightheadedness occurred from 20 to 45 min after i.m. injection.

Pain measurements

Ketamine prolonged the period of pain-free ischaemic exercise as shown by the mean pain scores at 15-s intervals (fig. 1) and by the "tourniquet times" (table I). In the period before drug administration the "tourniquet times" did not differ significantly from one another, and the pain scores were similar in all three groups; severe pain was experienced 75–90 s after inflation of the cuff. At 15 min after i.m. ketamine, the pain was graded none to mild at 90 s, and at 30 min after both i.m. and oral doses, the pain was mild to moderate at 90 s.

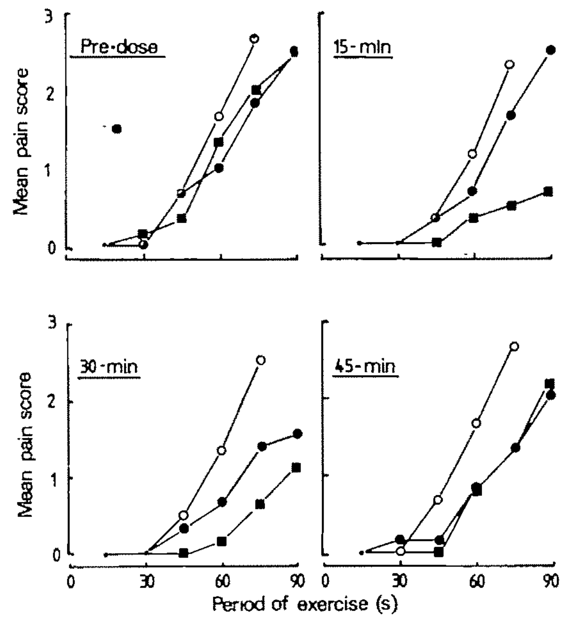

FIG. 1. Mean pain scores during ischaemic exercise of the arm in six subjects given ketamine 0.5 mg kg^{-1} i.m. (■) or orally (●). ○ = control; 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain.

Similarly, at 15 min following i.m. ketamine and at 30 min following both i.m. and oral doses, the "tourniquet time" was significantly prolonged. At all other times, and following placebo, the pain

TABLE I. *Times to reach intolerable pain during ischaemic exercise of the arm ("tourniquet times") (mean ± SEM) (s) (n = 6). †Not significantly different from control times before drug administration. **Significantly greater than times before drug administration (P < 0.05)*

Study	Before drug administration	Time after drug administration (min)				
		0	15	30	45	60
Control	88.7±2.7	98.7±2.9	89.2±3.5	90.0±3.1	87.0±3.2	88.8±2.8
Oral ketamine 0.5 mg kg^{-1}	99.0±5.9†	102.7±5.7	103.0±4.8	108.8±4.8**	106.0±7.6	101.0±7.9
I.m. ketamine 0.5 mg kg^{-1}	98.2±3.6†	101.3±5.9	122.2±7.9**	118.7±7.5**	104.3±6.2	103.0±7.8

scores and "tourniquet times" were similar to the values in the period before drug administration. Thus i.m. ketamine 0.5 mg kg^{-1} increased pain thresholds within 15 min of injection and lasted for a further 15–30 min, whereas, after oral ketamine in the same dose, analgesia was found only at 30 min after administration.

Pharmacokinetics

Absorption of ketamine after i.m. injection was rapid with apparent mean peak concentration of 240 ± 50 ng ml^{-1} occurring at 22 ± 4 min (table II). The estimated time between completion of injection and appearance of ketamine in plasma (lag time) was about 1 min and the mean absorption half-time was 8.2 min. In four subjects who had previously received an i.v. injection of ketamine 0.25 mg kg^{-1} the bioavailability, corrected for dose, was 93%. The mean terminal half-life ($T_{\frac{1}{2}}{}^{\beta}$) was 155 ± 12 min, which did not differ significantly from that after i.v. injection (Clements and Nimmo, 1981). Plasma concentrations of norketamine were smaller than those of ketamine for the 1st hour and the mean peak norketamine concentration of 90 ± 10 ng ml^{-1} occurred at 77 ± 14 min (fig. 2).

After oral administration, absorption was incomplete and was delayed, with a lag time of about 8 min. The mean peak plasma ketamine concentration was 45 ± 10 ng ml^{-1} and occurred after 30 ± 5 min (table III). The mean bioavailability in four subjects was 16.5% The mean peak norketamine concentration was 200 ± 44 ng ml^{-1} at 60 ± 13 min (fig. 3).

After i.m. ketamine, "tourniquet times" were prolonged and subjects experienced only mild pain after 75–90 s of ischaemic exercise when the mean plasma ketamine concentration was greater than 150 ng ml^{-1} and the mean plasma norketamine concentration was greater than 55 ng ml^{-1}. After oral ketamine the corresponding mean concentrations of ketamine and norketamine were

TABLE II. *Pharmacokinetic values in volunteers after i.m. injection of ketamine 0.5 mg kg^{-1}. — = Subjects not receiving i.v. injection of ketamine previously*

Subject	Peak concentration (ng ml^{-1})	Peak time (min)	Absorption rate constant (min^{-1})	Half-life (min)	Bioavailability (%)
DB	230	30	0.040	183	96.5
JC	140	30	0.049	114	92.3
FH	425	5	0.412	188	—
DL	335	15	0.285	134	97.2
WM	100	30	0.069	138	—
WN	230	20	0.142	172	85.9

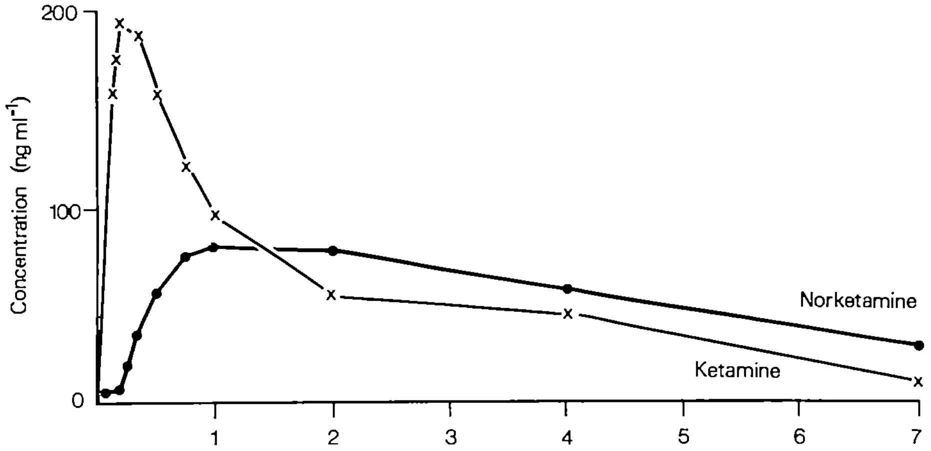

FIG. 2. Mean plasma ketamine and norketamine concentrations following administration of ketamine 0.5 mg kg^{-1} i.m. to six healthy volunteers.

TABLE III. *Pharmacokinetic values in volunteers after oral ingestion of solution of ketamine 0.5 mg kg^{-1}.—= Subjects not receiving i.v. injection of ketamine previously*

Subject	Ketamine Peak concn (ng ml^{-1})	Ketamine Peak time (min)	Norketamine Peak concn (ng ml^{-1})	Norketamine Peak time (min)	Bioavailability (%)
DB	30	45	190	60	14.5
JC	35	30	220	60	16.3
FH	15	45	65	120	—
DL	35	20	390	45	11.2
WM	80	20	165	30	—
WN	70	20	160	45	24.5

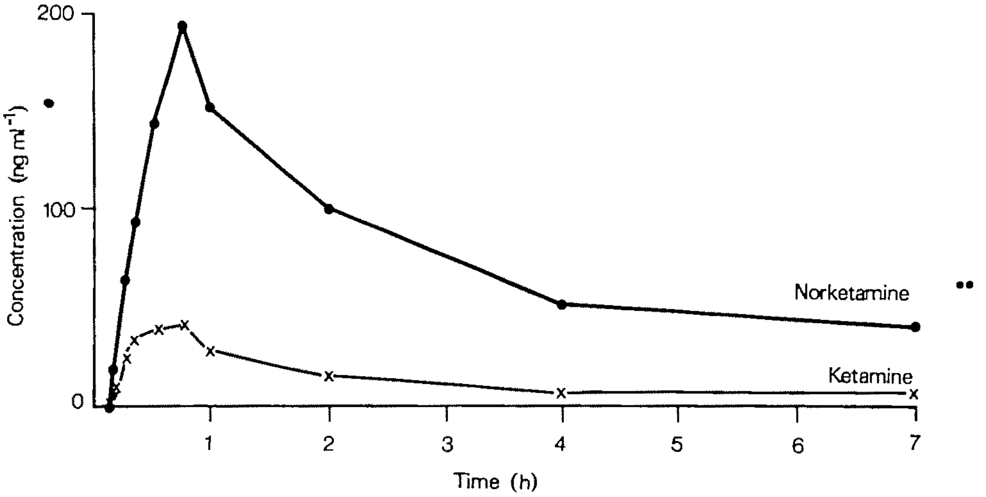

FIG. 3. Mean plasma ketamine and norketamine concentrations following administration of ketamine 0.5 mg kg^{-1} orally to six healthy volunteers.

40 ng ml^{-1} and 160 ng ml^{-1} respectively. There was, however, considerable interindividual variation.

DISCUSSION

In a previous study of patients and volunteers i.m. ketamine 0.44 mg kg^{-1} produced analgesia lasting 90 min (Sadove et al., 1971). Given i.m. in combination with pethidine, however, ketamine 30 mg produced no significant improvement on the analgesia of pethidine alone (Parkhouse and Marriott, 1977).

There appears to be no published work on the pharmacokinetics following i.m. administration of ketamine in either analgesic or anaesthetic doses or on the relationship between plasma concentration and effect. The appropriate i.m. dose has been established on an empirical basis leading to excessive doses being used for analgesia (Slogoff et al., 1974) and premedication (Rita and Seleny, 1974; Ryhanen, Kangas and Rantakyla, 1980) with resulting increase in frequency of psychic sequelae.

We have defined a mean plasma concentration which is associated with analgesia following i.m. injection (150 ng ml^{-1}). Previous workers have reported the plasma concentrations associated with awakening from ketamine anaesthesia. After 2.2 mg kg^{-1} i.v., consciousness returned when plasma concentrations were in the range of 700–1120 ng ml^{-1} (Little et al., 1972) whereas, after i.v. infusion, consciousness returned at plasma concentrations less than 640 ng ml^{-1} (Idvall et al., 1979). A range of plasma ketamine concentration exists, therefore, when analgesia occurs without unconsciousness.

The frequency of psychic sequelae appears to be dose-related (Dundee et al., 1970) and is markedly reduced with the use of ketamine in sub-anaesthetic doses (Chodoff and Stella, 1966; Akamatsu et al., 1974; Liang and Liang, 1975). It seems possible that, if plasma ketamine concentrations are kept within the analgesic range, these sequelae may be eliminated, even without sedative premedication.

I.m. administration avoids the very high peak concentrations produced by i.v. injection, which may be associated with hypertension.

The study also demonstrated an analgesic effect following oral ketamine 0.5 mg kg^{-1} despite a plasma concentration of only 40 ng ml^{-1}. However, the plasma norketamine concentration was very much larger than that observed after i.m. injection, and it seems likely that norketamine also has analgesic properties.

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PHARMACOCINETIQUE ET EFFETS ANALGESIQUES DE LA KETAMINE ADMINISTREE PAR VOIE INTRAMUSCULAIRE ET PAR VOIE BUCCALE

RESUME

La pharmacocinétique et les effets analgésiques de la kétamine administrée par voie intramusculaire et voie buccale en doses de 0,5 mg kg^{-1} ont été déterminés sur six volontaires en bonne santé. L'analgésie a été mesurée par le test du tourniquet à effort sous-maximal. Suivant les deux voies d'administration, la kétamine a prolongé la période d'exercice ischémique sans douleur. Les seuils de la douleur ont été portés à 15 min et à 30 min après l'injection intramusculaire, et à 30 min après l'administration de kétamine par voie buccale. La concentration de kétamine dans le plasma associée à l'analgésie a été de 150 ng ml^{-1} après la dose administrée par voie intramusculaire, mais seulement de 40 ng ml^{-1} après la dose administrée par voie buccale. L'administration par voie buccale a cependant été

associée à des concentrations beaucoup plus fortes du métabolite norkétamine, lequel peut avoir contribué à l'effet analgésique.

PHARMAKOKINETISCHE UND ANALGETISCHE EFFEKTE VON INTRAMUSKULÄR UND ORAL VERABREICHTEN KETAMIN-DOSEN

ZUSAMMENFASSUNG

Besagte Effekte bei Dosen von 0,5 mg kg^{-1} Ketamin wurden an 6 gesunden Freiwilligen untersucht. Die Schmerzlinderung wurde mittels des Abbindetests mit submaximaler Stärke gemessen. Sowohl nach oraler als auch bei intramuskulärer Verabreichung wurde die Periode schmerzfreier ischämischer Übungen durch Ketamin verlängert. Die Schmerzschwellen wurden 15 und 30 min nach intramuskulärer Injektion, und 30 min nach oraler Verabreichung von Ketamin erhöht. Die Plasma-Ketaminkonzentration bei Analgesie betrug 150 ng ml^{-1} nach der intramuskulären Dosis, aber nur 40 ng ml^{-1} nach der oralen Dosis. Die orale Verabreichung führte aber zu wesentliche grösseren Konzentrationen des Metaboliten Norketamin, was zu der schmerzlindernden Wirkung beigetragen haben mag.

EFECTOS FARMACOCINETICOS Y ANALGESICOS DE LA KETAMINA ORAL E INTRAMUSCULAR

SUMARIO

Se determinaron en seis voluntarios sanos los efectos farmacocinéticos y analgésicos de 0,5 mg kg^{-1} de ketamina oral e intramuscular. La analgesia se midió mediante la prueba de torniquete con efecto submaximal. A raíz de las dos rutas de administración, la ketamina prolongó el periodo de ejercicio isquémico sin dolor. Los umbrales de dolor se incrementaron a 15 y a 30 minutos después de la inyección intramuscular y a 30 minutos después de la ketamina oral. La concentración de ketamina en el plasma, asociada con la analgesia, fue de 150 ng ml^{-1}, a raíz de la dosis intramuscular, pero sólo de 40 ng ml^{-1} después de la dosis oral. La administración oral vino, sin embargo, asociada con concentraciones de la metabolita norketamina mucho más elevados, lo que puede haber contribuido al efecto analgésico.

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ANAESTHESIA FOR THE MORBIDLY OBESE

Experience with 110 patients

G. S. Fox, D. G. Whalley and D. R. Bevan

SUMMARY

The anaesthetic management and postoperative complications of 110 grossly obese patients undergoing weight-reducing surgery have been reviewed. The major problems were technical, related to the bulk of the patient, and respiratory, caused by alterations in pulmonary physiology. Extradural catheters were placed in 70 patients before induction of general anaesthesia. In all patients the trachea was intubated during anaesthesia and the lungs ventilated with large tidal volumes and appropriate inspired oxygen concentrations. Muscle relaxation was achieved with extradural block in 35 patients; the remainder received pancuronium i.v. Extradural analgesia with bupivacaine provided excellent analgesia after surgery and greatly facilitated nursing care.

Severe obesity is now considered a major nutritional problem in North America (Angel et al., 1978). Subjects may be described as grossly obese (Farebrother, 1979) if they appear to be very fat and their weight exceeds by more than 70% the ideal weight for their sex and height. This is associated with the greatest mortality for life insurance (Metropolitan Life Insurance Company, 1959).

Reduction in weight may be achieved surgically either by small bowel bypass procedures which short-circuit the intestine, or by gastroplasty which reduces the volume of the stomach and delays its emptying (Printen and Mason, 1973).

We have reported our experience with 18 patients who had bypass procedures and advocated a method of operative and postoperative care based on the use of continuous extradural analgesia (Fox, 1975). This report describes our experiences over 6 years with 110 grossly obese patients who underwent weight-reducing surgery.

Gross obesity is associated with major complications including severe respiratory abnormalities (Farebrother, 1979), hypertension and heart disease (Angel et al., 1978), abnormal glucose tolerance (Angel et al., 1978) and liver disease (Strunin, 1977).

We were particularly concerned with respiratory management of the patients after operation.

PATIENTS

Eighty-three female and 27 male patients (table I) with a mean age of 34.5 ± 9.5 yr and a mean weight of 134.5 ± 31.8 kg were studied. The heaviest patient weighed 218 kg. Small bowel bypass procedures were performed in 84 and gastroplasty in the remainder.

TABLE I. *Preoperative data: 110 patients (83 female) (mean ± SD)*

Weight (kg)	135 ± 32
Age (yr)	35 ± 10
Arterial pressure (mm Hg)	
Systolic	135 ± 25
Diastolic	86 ± 13
Abnormal e.c.g.	18
Abnormal glucose tolerance test	14
Abnormal chest x-ray	9
Haemoglobin (g dl^{-1})	14.8 ± 0.9
SGOT (u. litre^{-1})	33 ± 24
SGPT (u. litre^{-1})	46 ± 28
Small bowel bypass	84 patients
Gastroplasty	26 patients

Status before operation

Respiratory system. Many of the patients complained of dyspnoea on exertion and in some, mobility was minimal. Chest x-ray was abnormal in nine (table I). Spirometry in 37 patients demonstrated a mean forced vital capacity of 3.5 ± 0.7 litre and forced expiratory volume in 1 s ($FEV_{1.0}$) of 2.8 ± 0.5 litre. Blood-gas analysis breathing room air showed a mean Pa_{O_2} 10.4 ± 1.4 kPa, Pa_{CO_2} 4.97 ± 0.7 kPa and pH 7.42 ± 0.03 (table II). Only one patient was somnolent with sleep apnoea characteristic of the

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Pickwickian syndrome, although it has been estimated to occur in 10% of grossly obese subjects (Alexander, Amad and Cole, 1962). This patient underwent tracheotomy before operation. Two patients were receiving bronchodilator therapy.

Cardiovascular system. Mean systolic and diastolic arterial pressures were 134.5 ± 24.5 and 86.1 ± 13.2 mm Hg and only one patient was receiving antihypertensive therapy. Eighteen patients had some e.c.g. abnormality (table I) and one took nitroglycerin for angina. Fifteen patients were receiving diuretic therapy to encourage weight loss, but none for congestive cardiac failure.

Metabolic tests. Abnormal glucose tolerance tests were found in 14 patients; three were receiving oral hypoglycaemic agents and one was being treated with insulin. No gross disturbance of liver function was found. Mean serum concentrations of bilirubin (1.0 ± 0.42 μmol litre^{-1}) and liver enzymes (SGOT 32.6 ± 23.7 u. litre^{-1}, SGPT 46.4 ± 27.5 u. litre^{-1}) were within normal ranges. Mean haemoglobin concentration in 110 patients was 14.8 ± 0.9 g dl^{-1}.

ANAESTHETIC MANAGEMENT

Before operation

The occurrence of associated disease was determined at the preoperative visit. Physical examination included inspection of head and neck to anticipate difficulty in tracheal intubation, upper limbs for the insertion of i.v. cannulae and back for location of the lower thoracic and lumbar spines. Explanation of the perioperative care was given and arrangements made for breathing exercises and physiotherapy before and after surgery. As a group, the patients were particularly co-operative in complying with the physician's instructions. Premedication with an opiate and atropine was prescribed and heparin 5000 units s.c. ordered for patients who would not receive an extradural catheter.

Anaesthesia

An i.v. cannula and usually a lumbar extradural catheter were inserted on arrival in the operating room before induction of general anaesthesia. After 5 min preoxygenation, anaesthesia was induced with thiopentone 300–500 mg and tracheal intubation was facilitated with suxamethonium 100 mg.

Ventilation was controlled in all patients using a Ventimeter ventilator with nitrous oxide in oxygen; the tidal volume and fresh gas flow were set initially at about 30% greater than for patients of normal weight and then adjusted after blood-gas analysis. Lignocaine 300 mg in 2% solution with adrenaline 1 : 200 000 was injected before induction of anaesthesia in 35 of the small bowel bypass group which obviated the need for further analgesia or muscle relaxants (Bromage, 1978). Muscle relaxation was produced in the remainder with pancuronium; a single bolus of 8 mg usually being sufficient for the 2–3 h procedure, and analgesia was maintained either with intermittent pethidine or fentanyl or with inhalation agents, usually enflurane 0.5–1.5%. Neuromuscular blockers, when used, were antagonized with atropine and neostigmine at the end of the operation and the trachea was extubated in the operating room.

Monitoring throughout the operation included e.c.g. and arterial pressure (radial artery catheter inserted after induction). Samples for arterial blood-gas analysis were withdrawn from time to time.

Care after operation

All patients remained in an intensive care area for 24 h after operation. They were nursed in the semi-recumbent, 45° position, turned on either side every 2–3 h and breathed humidified 50% oxygen via a venturi-type mask. Intermittent deep breathing and leg movement were encouraged by the nursing staff. No patient received artificial ventilation after operation.

Seventy patients received analgesia via the extradural catheter through which 0.25% bupivacaine 7–12 ml was injected every 90–120 min by nursing staff. This agent, concentration and dose were chosen for their long duration of action and minimal motor blockade to allow pain-free deep breathing. Some of the initial patients received 1–2% lignocaine for analgesia. Hypotension was observed infrequently. Analgesia was provided in the remainder with intermittent doses of pethidine 50–100 mg i.m. except in five patients who requested none. Extradural analgesia was either ineffective or incomplete in four patients who received supplementary pethidine. There was little difference in postoperative blood-gas tensions between the extradural and narcotic groups. Breathing room air, mean Pa_{O_2} for the entire group was 8.6 (±1.7) kPa and Pa_{CO_2} was 5.1 (±0.7) kPa (table II). However, in those who were given extradural analgesia, Pa_{O_2} and Pa_{CO_2} were 9.0 (±1.5) kPa and 4.9 (±0.7) kPa. In comparison, the narcotic group had tensions of 8.0 (±1.3) kPa and 5.3 (1.1) kPa for oxygen and carbon dioxide respectively (table III). Most patients had a mild metabolic acidosis during and immediately after surgery. This has been recognized by others (Vaughan, Englehardt and Wise, 1974; Eriksen, Andersen and Rasmussen, 1977) although its aetiology is uncertain.

Patients were discharged from the recovery room on the day after surgery if satisfactory breathing could be achieved without extradural analgesia. The mean time in the recovery room was 21.1 ± 12.9 h.

TABLE II. *Blood-gas analysis (breathing air) (mean ± SD)*

	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)
Before operation	10.4 ± 1.4	5.0 ± 0.7
After operation		
All patients	8.6 ± 1.7	5.1 ± 0.7
Extradural group	9.0 ± 1.5	4.9 ± 0.7
Narcotic group	8.0 ± 1.3	5.3 ± 1.1

TABLE III. *Postoperative complications in 110 patients*

	Total	Extradural analgesia	Narcotic analgesia	Surgical procedure	
				Bowel bypass	Gastroplasty
Pulmonary embolism	5	4/70 (5.7%)	1/40 (2.5%)	5/84 (5.9%)	0/26 (0%)
Uncontrolled diabetes	3	2/70 (2.9%)	1/40 (2.5%)	3/84 (3.6%)	0/26 (0%)
Wound infection or dehiscence	9	6/70 (8.6%)	3/40 (7.5%)	7/84 (8.3%)	2/26 (7.2%)
Pneumonia	4	2/70 (2.9%)	2/40 (5%)	4/84 (4.3%)	0/26 (0%)
Lung collapse	24 (21.8%)	13/70 (18.5%)	11/40 (27.5%)	19/84 (22.6%)	5/26 (19.2%)

COMPLICATIONS

An attempt was made to determine the frequency of pulmonary and metabolic complications after surgery (table III). Chest x-ray demonstrated lung collapse in 18.5% of patients who had extradural analgesia and in 27.5% who received narcotics. Lung collapse was common in heavier patients with reduced lung volumes and oxygen tensions before operation, but was not influenced by site of operation. Five patients, all in the bowel bypass group, had a suspected pulmonary embolus, and one of them died. Pneumonia, diagnosed on clinical and x-ray appearances, occurred in only four patients although a temperature greater than 38 °C was observed in 75% of patients after small bowel bypass and in 46% after gastroplasty.

It was necessary to administer insulin for the control of blood sugar in three patients. Wound infection or disruption occurred in nine patients.

DISCUSSION

The major anaesthetic problems of grossly obese patients are technical difficulties imposed by the bulk of the patient, maintenance of adequate respiratory function during and after surgery and continued treatment of associated diseases such as diabetes mellitus, hypertension and myocardial ischaemia.

Technical problems

Transfer of the patient from bed to operating table required the help of people or special lifting apparatus. Identification of veins and arteries for cannulation was time consuming because they were not easy to see or feel and, even when identified, their depth was difficult to judge. Similarly, landmarks for regional anaesthetic techniques were vague and ill-defined. Tracheal intubation required considerable technical ability because the neck was often concealed beneath rolls of fat and the fleshy soft tissues tended to engulf the laryngoscope blade.

In the period after operation, the patient's bulk hindered positioning by the nursing staff and electrically operated adjustable beds were used. Cardiorespiratory monitoring was complicated because the weight obscured respiratory movement of the chest and caused errors in sphygmomanometry. Chest radiography required large films if the whole of the lung fields were to be included.

Respiratory problems

Obese patients suffer significant changes in pulmonary function. Hypoxaemia may exist before operation and may increase during surgery and in the recovery period after operation. The most significant abnormality is a decrease in functional residual capacity (FRC), caused essentially by reduction in expiratory reserve volume (ERV; fig. 1) so that closing capacity (CC) exceeds FRC during tidal breathing (Holly et al., 1967). This change in FRC/CC and the associated reduction in Pa_{O_2} occurs when the obese patient is in the supine position, but may be present in the markedly obese in the sitting position. Before operation mean sitting Pa_{O_2} of 10.4 (1.4) kPa was less than normal in our patients, but was similar to values noted by Vaughan, Englehardt and Wise (1974) in obese patients.

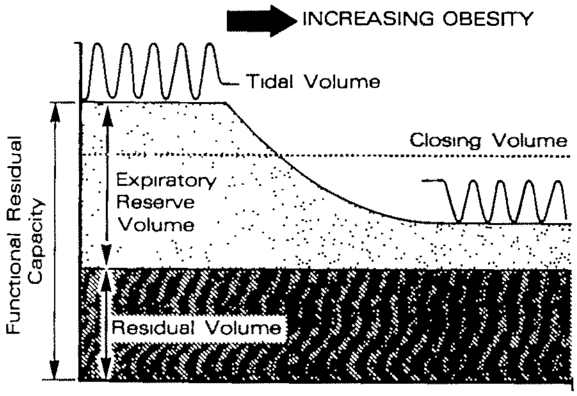

FIG. 1. Expiratory reserve volume is decreased by gross obesity and tidal ventilation occurs below closing volume (from Fox, 1975 with permission).

In both normal (Don, Wahba and Craig, 1972) and obese (Hedenstierna, Santesson and Norlander, 1976) patients, further reductions in FRC and Pa_{O_2} occur during and after anaesthesia. Some obese subjects required FI_{O_2} 0.5 to maintain Pa_{O_2} at 10 kPa during mechanical ventilation (Hedenstierna, Santesson and Norlander, 1976). Transient reductions in Pa_{O_2} may also occur when the abdominal wall is retracted (Tsueda, Pugh and Boyan, 1976) or when the patient is placed in the Trendelenberg position (Vaughan and Wise, 1976).

In obese patients, Eriksen, Andersen and Rasmussen (1977) demonstrated that vital capacity and Pa_{O_2} decreased after jejuno-ileal bypass. Vaughan, Bauer and Wise (1976) showed that Pa_{O_2} was reduced from the preoperative value, particularly if the patient was nursed in the supine position.

Rørvik and Bø (1976) have shown that deep breathing improved Pa_{O_2} in awake obese subjects, possibly by opening closed lung units and improving ventilation/perfusion relationships. Large tidal volume ventilation was used in our study with no positive end-expiratory pressure (PEEP). Eriksen and others (1978) have shown that in obese subjects PEEP reduced cardiac index by approximately 20% and a similar improvement in oxygenation could be achieved with large tidal volumes. Indeed, Söderberg, Thomson and White (1977) found that PEEP reduced Pa_{O_2} in obese subjects during anaesthesia.

Extradural analgesia

Maintenance of optimum analgesia and oxygenation and prevention of further respiratory impairment is the aim of any post-operative regimen. We attempted to achieve these objectives by the use of extradural analgesia. Vital capacity (Miller et al., 1976), FRC (Alexander et al., 1973) and oxygen tension can be improved in non-obese patients with extradural block. Eriksen, Andersen and Rasmussen (1977) noted, in obese patients during the initial period after operation, a mean decrease in oxygen tension of 3.4 kPa with narcotic analgesia while breathing room air. This compares to mean decreases of 1.4 kPa and 2.4 kPa with extradural and narcotic analgesia in this series. In addition, oxygen tensions were maintained with a combination of humidified oxygen and chest physiotherapy and by nursing the patients in the semi-recumbent position.

Extradural analgesia was provided by continuous blockade with 0.25% bupivacaine 7–12 ml every 1.5–2 h. The extradural catheter was inserted before induction of general anaesthesia while the patient was in the sitting position. Occasionally, a long 14-cm, 16-gauge Tuohy needle was inserted to the extradural space. Continuous extradural analgesia after operation reduced wound pain and allowed patients to cough, perform vigorous leg exercises, turn from side to side and in some cases, sit up during the early recovery period. Early mobilization and frequent leg movements at this time were considered to be important in our patients because heparin s.c. for the prophylaxis of deep vein thrombosis and pulmonary embolus was omitted lest haemorrhage occur into the extradural space (Varkey and Brindle, 1974).

Decrease in pain and abdominal splinting allowed patients to enjoy large tidal volume ventilation which has been shown to improve, at least temporarily, arterial oxygenation (Holly et al., 1967; Rørvik and Bø, 1976; Eriksen, Andersen and Rasmussen, 1977). Well established extradural blockade maintains constant analgesia, while the effects of i.m. narcotics are variable in normal subjects and are dependent on the rate of administration and absorption (Mather et al., 1975). The optimun dose and pharmacokinetics of narcotics in the obese are unknown.

Associated diseases

The majority of our patients had no pulmonary or cardiovascular abnormalities before operation, except for low arterial oxygen tensions. In a series of 37 patients awaiting surgery and who were 100% overweight, Andersen, Rasmussen and Eriksen (1977) found no abnormalities other than arterial hypoxaemia. $FEV_{1.0}$ was reduced to values similar to ours, but considered to be within the normal range. Söderberg, Thomson and White (1977) found normal $FEV_{1.0}$ and maximum voluntary ventilation before operation.

In our series of relatively young patients, none suffered from severe cardiac or metabolic disease and only one displayed the Pickwickian syndrome. Diabetes mellitus was uncommon and there was no evidence of liver dysfunction from routine liver function tests.

Complications

Lung collapse was more common in the heaviest patients and in those with smaller lung volumes before surgery, but there was no difference in its frequency between patients who had small bowel bypass or gastroplasty. However, the overall frequency of collapse in our series (22%) was much greater than the 9% reported in obese patients undergoing duodenal ulcer surgery (Postlewait and Johnson, 1972). Söderberg, Thomson and White (1977) found that eight of 17 patients developed atelectasis after operation, and that these patients were the heaviest.

Five patients (4.5%) who had evidence of pulmonary embolism were in the extradural bypass group. This frequency is similar to that noted by Printen and Mason (1973) following gastroplasty (6%). The low frequency of pneumonia is similar to that noted by Postlewait and Johnson (1972) in obese patients.

Nine patients (8.1%) in our series had wound infections after operation. This was less than the 18% noted by Printen and Mason (1973) following gastroplasty and the 28% noted in diabetic obese patients (Postlewait and Johnson, 1972) but is similar to that noted by others (Printen, Paulk and Mason, 1975; Pemberton and Manax, 1971).

The difference between this group of obese patients and previously reported series is the extensive use of extradural analgesia for pain relief after operation. In all our patients the tracheal tube was removed immediately after surgery and adequate respiratory function was maintained with spontaneous ventilation. Thus, routine postoperative controlled ventilation as advocated by others (Paul, Hoyt and Boutros, 1976; Söderberg, Thomson and White, 1977; Bendixen, 1978) appears to be unnecessary and may complicate respiratory and nursing care by limiting the patients' ability to co-operate.

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ANESTHESIE POUR LES OBESES MORBIDES

Expérience portant sur 110 patients

RESUME

Les soins anesthésiques et les complications postopératoires survenues à 110 patients fortement obèses ayant subi une intervention chirurgicale afin de réduire leurs poids, sont passés en revue dans cet article. Les principaux problèmes rencontrés ont été d'ordre technique, (ils étaient reliés à la masse du patient) et d'ordre respiratoire, du fait des modifications survenues dans leur physiologie pulmonaire. On a placé des cathéters extraduraux à 70 patients avant l'induction de l'anesthésie générale. Chex tous les malades, la trachée avait été intubée pendant l'anesthésie et leurs poumons ont été ventilés à l'aide d'importants volumes d'air expiré et de concentrations appropriées d'oxygène inspiré. La relaxation musculaire de 35 patients a été obtenue par blocage extradural; alors que l'on a administré aux autres du pancuronium par voie intraveineuse. L'analgésie extradurale par la bupivacaïne a assuré une excellente analgésie après l'opération et grandement facilité les soins postopératoires.

ANÄSTHESIE FÜR SCHWER FETTLEIBIGE PATIENTEN

Erfahrungen mit 110 solcher Patienten

ZUSAMMENFASSUNG

Narkosedurchführung und postoperative Komplikationen bei 110 schwer fettleibigen Patienten, an denen gewichtsverringernde Operationen vorgenommen wurden, wurden analysiert. Die Hauptprobleme waren technischer Art, bezogen auf den Umfang der Patienten, und respiratorischer Art, bewirkt durch Änderungen der Lungenphysiologie. Extradurale Katheter wurden in 70 Patienten vor Beginn der allgemeinen Narkose eingeführt, und bei allen war ein Trachealrohr eingeführt, während die Lungen während der Narkose stark belüftet wurde—mit entsprechend hohen Sauerstoffkonzentrationen. Muskelentspannung wurde durch einen extraduralen Block bei 35 Patienten erzielt; die anderen erhielten Pancuronium intravenös. Extradurale Analgesie bewährte sich ausgezeichnet postoperativ und pflegeerleichternd.

ANESTESIA PARA EL PELIGROSAMENTE OBESO

Una experiencia con 110 pacientes

SUMMARIO

La gestión anestésica y las complicaciones posoperativas de 110 pacientes exageradamente gruesos que fueron sometidos a operaciones quirúrjicas encaminadas a la reducir del peso se han revisado. Los mayores problemas fueron de tipo técnico, debido a la enormidad del paciente, y de tipo respiratorio, ocasionados por las variaciones en la fisiología pulmonar. Se colocaron cáteteres extradurales en 70 pacientes antes de la inducción de la anestesia general. En todos los pacientes se intubó la tráquea durante la anestesia y se ventilaron los pulmones con grandes volúmenes periódicos y con apropiadas concentraciones de oxígeno inspirado. En 35 pacientes se consiquió relajación muscular con bloqueo extradural; el resto recibió pancuronio intravenoso. La analgesia extradural con bupivacaína provee una excelente analgesia después de la operación quirúrjica y facilitó en gran medida los cuidados posteriores.

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POSTOPERATIVE SPINAL ANALGESIA WITH MORPHINE

K. SAMII, M. CHAUVIN AND P. VIARS

SUMMARY

Patients with pain after operation received morphine hydrochloride intrathecally in doses of 0.02 mg kg^{-1} ($n = 30$) and 0.2 mg kg^{-1} ($n = 30$). The high-dose group showed slightly longer-lasting and more potent analgesia than the low-dose group. Sedation, decreases in heart rate and systolic arterial pressure, oliguria, nausea and urinary retention were more frequent in the high-dose group. Two patients of the high-dose group showed evidence of respiratory depression which appeared after a late change in posture (7 and 11 h). We conclude that postoperative analgesia with intrathecal morphine 0.02 mg kg^{-1} must be followed by a prolonged head-up posture and be performed in hospital units where the treatment of respiratory depression is competent.

A direct spinal action of narcotic drugs was demonstrated in animals by Yaksh and Rudy (1976) and confirmed in man by Wang, Nauss and Thomas (1979) who showed that, when given intrathecally, morphine produced analgesia without central depression. However, the dose of morphine used in that study was much less than that used previously by us (Samii et al., 1979) (0.5–1.0 mg and 20 mg respectively). Therefore, it was decided to compare, in a double-blind study, the effects of morphine 0.02 mg kg^{-1} and 0.2 mg kg^{-1} administered intrathecally in the treatment of postoperative pain and to determine the dose most appropriate for clinical use.

PATIENTS AND METHODS

A double-blind study was undertaken in which 30 patients received morphine hydrochloride 0.02 mg kg^{-1} and a further 30 patients received morphine hydrochloride 0.2 mg kg^{-1}. All patients gave informed consent for the study. The inclusion of a third group receiving a placebo intrathecally (10% dextrose solution without morphine) was abandoned after treatment of three patients because of the absence of analgesia and the risks of intrathecal puncture. Morphine was injected intrathecally at least 4 h after the last systemic injection of narcotic (fentanyl), using a 25-gauge spinal needle passed through an introducer. The morphine solution was made hyperbaric by the addition of the same volume of 10% dextrose and the volume of the solution injected was always less than 2 ml. Immediately after the intrathecal injection the patients were placed in a 40-degree head-up position and kept in the recovery room which is open day and night. The following indices were measured at least once every hour for 6 h and then once every 3 h by one of two observers who was unaware of the dose of morphine used: heart rate, systolic arterial pressure, respiratory frequency, urinary output, intensity of pain, upper level of analgesia (pinprick), discrimination of light touch, motor function (active elevation of the lower limbs) and sedation. End-tidal carbon dioxide concentration (infra-red analyser) was always measured when sedation was observed. When pain reappeared the patients were moved from the recovery room to their own room where they were observed for at least 5 days to exclude late side-effects. Comparisons between the two groups were performed using Student's t test for the duration of analgesia, Mann and Whitney test for the intensity of pain and χ^2 test for the percentage of patients.

RESULTS

The degree of postoperative pain (scored as: nil = 0, very mild = 1, mild = 2, moderate = 3, severe = 4, intolerable = 5), the types of surgical incision and the ages of the patients were similar in both groups (table I). Table II summarizes the effects of the administration of morphine in the two groups.

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TABLE I. *Clinical data of the patients studied. No statistically significant differences between groups*

	Dose of morphine (mg kg^{-1})	
	0.02 ($n = 30$)	0.2 ($n = 30$)
Age (yr) (mean ± SD)	53 ± 8	57 ± 9
Laparotomy	28	25
Thoracotomy	6	7
Mean initial intensity of pain (scored 0–5)	3.9	4.3

TABLE II. *Consequences of intrathecal administration of morphine. Value denotes number of patients unless stated otherwise*

	Dose of morphine (mg kg^{-1})		
	0.02 ($n = 30$)	0.2 ($n = 30$)	P
Mean maximal decrease in pain (scored 0–5)	3.1	4.0	<0.05
Duration of analgesia (h) (mean ± SD)	26 ± 3	33 ± 4	<0.01
Sedation	18	28	<0.01
Respiratory frequency < 10 b.p.m.	0	2	n.s.
End-tidal $CO_2 > 5.5\%$	0	2	n.s.
Decrease in heart rate ⩾ 20 beat min^{-1}	3	1	<0.02
Decrease in systolic arterial pressure ⩾ 20 mm Hg	5	14	<0.02
Urinary output < 150 ml per 3 h despite plasma volume expansion	16	25	<0.02
Nausea	0	5	<0.02
Urinary retention without previous urethral catheter	2/19	14/15	<0.001
Cephalgia	0	1	n.s.

Analgesia

Following the intrathecal injection, analgesia appeared in both groups after 10–15 min and was maximum after 2–3 h. A segmental limit of hypalgesia to pin-prick, ranging from dermatomes T1 to T7, could be detected in all patients. The moment when there was an increase in the intensity of pain of at least 1 point (scored 0–5) was taken as the end of analgesia.

Sedation, respiratory frequency and end-tidal carbon dioxide concentration

Sedation was more frequent in the morphine 0.2 mg kg^{-1} group than in the morphine 0.02 mg kg^{-1} group. Sedation appeared between 2 and 6 h after administration and lasted from 6 to 12 h. All but two patients with sedation had respiratory frequency of less than 10 b.p.m. and end-tidal carbon dioxide concentration greater than 5.5%. Indeed, two patients of the morphine 0.2 mg kg^{-1} group who were changed to the horizontal position 7 h and 11 h respectively after the injection of morphine had slowing of breathing (8 b.p.m. and 6 b.p.m.) and increases in end-tidal carbon dioxide concentration (6.5% and 7.2%). These effects were immediately reversed by naloxone 0.4 mg i.v. while analgesia persisted (pain score: 1 and 0 respectively). A continuous infusion of naloxone 0.4 mg h^{-1} was instituted (for 9 h and 6 h respectively) to prevent the recurrence of respiratory depression.

Heart rate, systolic arterial pressure and diuresis

The changes in these vital signs were considered significant if no obvious cause of hypovolaemia such as haemorrhage or fluid loss was observed. Decreases in heart rate equal to or greater than 20 beat min^{-1} and in systolic arterial pressure of at least 20 mmHg were more frequent in the morphine 0.2 mg kg^{-1} group than in the other group. However, heart rate and systolic arterial pressure remained always greater than 60 beat min^{-1} and 100 mm Hg respectively. Urinary output of less than 150 ml per 3 h was considered significant if it persisted despite the rapid infusion of lactate Ringer's solution 1000 ml in 30 min. Oliguria was more frequent in the morphine 0.2 mg kg^{-1} group than in the morphine 0.02 mg kg^{-1} group. In all the oliguric patients urinary output could be increased with frusemide 20 mg i.v. Changes in heart rate, systolic arterial pressure and diuresis appeared from 2 to 4 h after morphine injection.

Nausea

Nausea was only observed in five patients of the morphine 0.2 mg kg^{-1} group. It was treated successfully by the administration of droperidol 2.5–5 mg i.v.

Urinary retention

This was rare in the morphine 0.02 mg kg^{-1} group and observed in all but one of the patients of the morphine 0.2 mg kg^{-1} group and required insertion of a catheter in these patients.

Headache

Headache was observed in only one patient in the morphine 0.2 mg kg^{-1} group, occurring on the day following the intrathecal injection and easing spontaneously.

Sensitivity to light, touch and motor function remained unchanged.

DISCUSSION

Our results show that morphine 0.2 mg kg^{-1} given intrathecally produced slightly longer-lasting relief of pain, but was associated with more frequent side-effects than the 0.02-mg kg^{-1} dose.

In this study morphine was given as mg kg^{-1} of an absolute dose to permit a simultaneous pharmacokinetic study of plasma concentration and urinary elimination of morphine. This study is not yet complete.

The presence of a detectable upper thoracic level of analgesia was not reported in earlier studies of this technique (Wang, Nauss and Thomas, 1979), but constitutes a powerful argument for the direct spinal action of morphine when given intrathecally. However, it does not exclude an action at other sites. On the contrary, several of the side-effects observed suggest a simultaneous involvement of the opiate receptors in the central nervous system. In all but two of the patients who became sleepy, respiratory frequency and end-tidal carbon dioxide concentration were within normal limits. However, the absence of blood-gas data and carbon dioxide response curves in our study does not permit us to eliminate a certain degree of respiratory depression. We can only conclude that, even if present, the respiratory depression was not dangerous except in two patients.

The persistence of analgesia following the injection of naloxone and the improvement in ventilation are a probable result of lower concentrations of morphine near the respiratory centres than in the vicinity of the spinal cord, and may be associated with the local analgesic action of intrathecal morphine. The decrease in heart rate and in systolic arterial pressure may have been caused by analgesia suppressing sympathetic stimulation. However, these cardiovascular changes were more frequent in the morphine 0.2 mg kg^{-1} group, whereas analgesia was good in both groups. Thus, a direct inhibitor action of morphine on higher sympathetic centres is a possible explanation for these cardiovascular changes. The oligiura we observed may have been caused by renal hypoperfusion. However, the absence of severe hypotension and the persistence of oliguria despite plasma volume expansion eliminate this hypothesis: hypersecretion of antidiuretic hormone from a direct central action of morphine may explain this finding, but a more detailed study is necessary for confirmation. Nausea is another side effect probably caused by the invasion of higher centres by the morphine. Wang, Nauss and Thomas (1979) did not observe similar side-effects with doses of morphine 0.5–1.0 mg, that is doses close to 0.02 mg kg^{-1}. However, that study involved only eight patients and the vital signs were recorded for 1 h, while most of the side effects we observed appeared at least 2 h after the injection. The respiratory depression observed in two patients in the morphine 0.2 mg kg^{-1} group occurred following a change in posture. Similar respiratory depression has been reported with 15 mg (Liolios and Andersen, 1979), 5 mg and 3 mg of morphine (Glynn et al., 1979). In all these reports two factors were present: a change in posture, even if late, or the previous systemic injection of narcotics (Glynn et al., 1979; Liolios and Andersen, 1979) or both. Urinary retention has been reported following the extradural injection of morphine (Bapat, Kshirsagar and Bapat, 1979). The urinary retention was frequent in the morphine 0.2 mg kg^{-1} group. A local-anaesthetic effect may occur with high dose of intrathecal pethidine (Cousins et al., 1979) and may be the explanation. On the other hand, a central mechanism can also be invoked. The use of a 25-gauge spinal needle probably explains the occasional occurrence of headache in the patients studied despite the prolonged head-up position. The normal muscular activity that this technique of spinal analgesia permits is particularly useful in the period after laparotomy or thoracotomy because it permits breathing exercises. The extradural injection of morphine also produces analgesia without central depression and may allow repeated injections through a catheter (Behar et al., 1979). The intrathecal procedure has the advantages of being technically easier than the extradural technique and a single injection produces pain relief of sufficient duration for most postperative patients. Pain following abdominal or thoracic surgery is much less by the 2nd day after operation. However, a prolonged head-up position may be difficult to maintain in the period after operation. Thus, the respective indications for extradural and intrathecal methods of analgesia have to be clarified by a comparative study.

We confirm that the intrathecal injection of morphine produces good and long-lasting pain relief after operation without major respiratory depression. However, the intrathecal administration of the dose of 0.02 mg kg^{-1} of morphine that we recommend must be made at least 4 h after any systemic injection of narcotic and be associated with a head-up position for at least 12 h. Naturally, the management of such patients should be undertaken in an intensive care unit or a recovery room where the assessment and treatment of any respiratory depression is possible.

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ANALGESIE RACHIDIENNE POSTOPERATOIRE A LA MORPHINE

RESUME

Des patients ressentant des douleurs après une intervention chirurgicale ont reçu intrathécallement des doses d'hydrochlorure de morphine de 0,02 mg kg^{-1} ($n = 30$) et de 0,2 mg kg^{-1} ($n = 30$). Le groupe ayant reçu la plus forte dose a affiché une analgésie légèrement plus puissante et de plus longue durée que le groupe ayant reçu la dose la plus faible. La sédation, la baisse de la fréquence cardiaque et de la pression systolique artérielle, l'oligurie, les nausées et la rétention d'urine ont été plus fréquents avec le groupe ayant reçu la forte dose. Deux patients ayant reçu la forte dose ont souffert d'une dépression respiratoire qui est survenue après un changement tardif de position (7 et 11 h). Nous en concluons que l'analgésie postopératoire à l'aide de morphine par voie intrathécale à raison de 0,02 mg kg^{-1} doit être suivie par une position prolongée avec tête relevée et n'être effectuée que dans les hôpitaux compétents pour administrer les soins nécessaires à toute dépression respiratoire.

POSTOPERATIVE SPINALANALGESIE MIT MORPHIUM

ZUSAMMENFASSUNG

Patienten mit postoperativen Schmerzen erhielten intrathecale Morphiumdosen von 0,02 mg kg^{-1} ($n = 30$) und 0,2 mg kg^{-1} ($n = 30$). Die Gruppe mit hoher Dosis erfuhr etwas länger und stärker wirkende Schmerzlinderung. In dieser Gruppe waren Sedierung und Abstiege in Herztätigkeit, systolischem Arteriendruck, Oligurie, Harnverhaltung und Übelkeit häufiger. Zwei Patienten dieser Gruppe zeigten Anzeichen respiratorischer Dämpfung nach einer späten Haltungsänderung (nach 7 und 11 Stunden). Wir schliessen, dass postoperative Morphium-Analgesie mit 0,02 mg kg^{-1} von einer längeren Haltung mit hochliegendem Kopf gefolgt und in einem Krankenhaus durchgeführt werden muss, in dem man gute Erfahrungen mit der Behandlung respiratorischer Dämpfungen hat.

ANALGESIA POSOPERATIVA DE LA ESPINA MEDIANTE MORFINA

SUMARIO

Aquellos pacientes que sufrieron dolor después de la operación recibieron hidrocloruro de morfina intratecalmente, en dosis de 0,02 mg kg^{-1} ($n = 30$) y 0,2 mg kg^{-1} ($n = 30$). El grupo de la mayor dosis mostró una analgesia ligeramente más poderosa y de mayor duración que el grupo que recibió la dosis menor. El grupo que recibió la mayor dosis presentó con más frecuencia casos de sedación, disminuciones del ritmo cardiaco y presión arterial sistólica, oliguria, nauseas y retención de la orina. Dos de los pacientes pertenecientes al grupo de la mayor dosis mostraron evidencia de depresión respiratoria, la cual apareció después de un cambio de postura tarde (7 a 11 h). Concluimos que la analgesia posoperativa mediante 0,02 mg kg^{-1} de morfina intratecal debe ser seguida por un prolongado periodo en el que la cabeza esté elevada y que debe efectuarse en las unidades del hospital en las que el tratamiento de la depresión respiratoria es competente.

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PREMEDICATION OF CHILDREN WITH TRIMEPRAZINE TARTRATE

R. G. B. BRAMWELL AND M. L. M. MANFORD

SUMMARY

A double-blind trial was undertaken to compare the effects of trimeprazine tartrate (2 mg kg^{-1} or 4 mg kg^{-1}) plus atropine 0.03 mg kg^{-1} for oral premedication of 192 children undergoing tonsillectomy. Demeanour before operation, side-effects after operation, recovery times and fluid balance were studied. Behaviour in the anaesthetic room and restlessness after operation were unaffected by the dose given. There was less vomiting associated with 4 mg kg^{-1} compared with 2 mg kg^{-1}. Prolonged recovery times occurred frequently in the two groups, 14% in the small- and 17% in the large-dose groups taking more than 10 h to recover full mental faculties. Fluid balance was unaffected by the dose and prolonged recovery did not result in a reduction of urine output. Trimeprazine tartrate is not recommended for routine premedication when early recovery is required.

Although trimeprazine tartrate (Vallergan) has been widely used for oral premedication in children since 1959 (Cope and Glover, 1959), general agreement has not been reached on a standard dose nor on the frequency of side-effects.

Trimeprazine tartrate has been used extensively in Queen Mary's Hospital for Children since 1961, generally in a dose of 4 mg kg^{-1} to a maximum of 120 mg (20 ml). Some children have found this relatively large volume and dose unpalatable especially if repeated for several anaesthetics, and this has sometimes led to refusal to take, or vomiting of, the dose. Occasionally, return to full consciousness after operation has been prolonged and some "day-case" patients have been too drowsy to be discharged home as planned. Early recovery may also be desirable to permit patients to take and retain fluids after operation. It would be beneficial if the use of a smaller dose of trimeprazine tartrate resulted in shorter recovery time and fewer side-effects without detriment to satisfactory sedation before operation.

This study evaluated the effects of oral premedication with trimeprazine tartrate 2 or 4 mg kg^{-1} on behaviour of children before operation, the frequency of postoperative side-effects and on postoperative recovery times and fluid balance.

PATIENTS AND METHODS

One hundred and ninety-two children aged 2–10 yr undergoing tonsillectomy with or without adenoidectomy, myringotomy or examination of ears were in a double-blind trial.

Each child was seen before operation by one of the authors (M.L.M.M.) who also gave or supervised the anaesthetic. Patients undergoing surgery in the morning received a 200-ml glucose drink at 5 a.m. while patients for afternoon lists had a light breakfast and a glucose drink at 10 a.m.

Two matching syrups were prepared containing trimeprazine tartrate 3 mg or 6 mg ml^{-1}. The syrups were put into numbered bottles on a random basis and used sequentially, the code remaining in a sealed envelope until the trial was completed and the results analysed. The syrups and codes were prepared and supplied to Queen Mary's Hospital pharmacy by May and Baker Ltd. Each child received 0.66 ml of syrup per kg body weight, giving either 2 mg kg^{-1} (small-dose group) or 4 mg kg^{-1} (large-dose group) of trimeprazine tartrate. The dose was calculated to the nearest 0.5 ml. Atropine sulphate solution 0.03 mg kg^{-1} was added and the mixture given orally 1.5–2 h before operation.

Induction and maintenance of anaesthesia were as described in a previous study (Boyd and Manford, 1973). Inhalation induction with cyclopropane or halothane was given to all those who had been promised this at the preoperative visit. I.v. induction with thiopentone 4–5 mg kg^{-1} (methohexitone for one patient with asthma) was given if requested by patients older than 5 yr. If the

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patient was less than 5 yr, an assessment was made of whether i.v. or inhalation induction would be less traumatic. The trachea was either intubated following administration of suxamethonium and anaesthesia maintained with halothane (151 patients) or ether was given by insufflation through a Boyle Davis gag (41 patients), depending on the surgeon's preference. After operation, analgesia was provided with dihydrocodeine tartrate 1–1.25 mg kg^{-1} (170 patients) or pethidine 1.5 mg kg^{-1} and promethazine 0.75 mg kg^{-1} (20 patients).

The children were cared for before and after surgery by the same small team of staff in the ward attached to the operating theatres. All but three patients in the trial remained in this ward until the morning after operation. The method of assessment of the effects of the premedication was based on Doughty (1959) and the relevant aspects of each child's response during the trial were recorded. The patient's behaviour in the anaesthetic room and response to induction were assessed by the anaesthetist and recorded under "demeanour in the anaesthetic room" as *satisfactory* if the patient was asleep or calm and co-operative, but *unsatisfactory* if the patient was apprehensive, tearful, noisy or unco-operative. Observations after operation were made by the nursing staff under the supervision of one of the anaesthetists. The patient's heart rate was recorded every 15 min; if awake at this time or if a drink was requested, the patient was asked to sit up. Waking time was defined as the length of time from premedication until the child could stay sitting securely and appeared alert. Fluid intake and urine output were measured from the time of premedication until the child left the postoperative ward on the following morning. Urine specimens were tested for ketones using "Labstix".

The results were evaluated statistically using a difference of means test or chi-squared test with Yates' correction, as appropriate, with 95% confidence limits.

RESULTS

Table I shows the details of patients in each group. There was no significant difference between the two groups with respect to age, sex, weight distribution or anaesthetic technique used.

Demeanour in anaesthetics room (table II)

There was no significant difference in anaesthetic room demeanour between the small- and large-dose groups whether i.v. or inhalation induction was used.

Postoperative observations (table III)

If the patient vomited once or twice, this was classified as mild; three or more vomits was

TABLE I. *Details of operations and anaesthetics*

	Small-dose group	Large-dose group
No. of patients	92	100
Sex		
Male	47	54
Female	45	46
Age (yr)		
Mean	6.08	5.9
Range	2–10	3–10
Weight (kg) (mean ± SD)	22.26 ± 4.42	21.47 ± 4.72
Induction		
Inhalation	58	71
I.v.	34	29
Maintenance		
Halothane	77	74
Ether	15	26

TABLE II. *Anaesthetic room demeanour*

		Deameanour	
Group	Induction	Satisfactory	Unsatisfactory
Small-dose	Inhalation	54	4
	I.v.	19	15
Large-dose	Inhalation	68	3
	I.v.	18	11

TABLE III. *Postoperative side-effects*

		Vomiting				
Group	Induction	None	Mild	Severe	Pallor	Restlessness
Small-dose	Inhalation I.v.	53	22	17	11 4 } 16%	24 (26%)
Large-dose	Inhalation I.v.	74	21	5	22 2 } 24%	19 (19%)

classified as severe. There was significantly less vomiting in those children who had received the larger dose of trimeprazine ($P < 0.01$).

Thirty-nine patients in the small-dose group vomited, the vomitus consisting mainly of blood on all but six occasions. Twenty-six patients in the large-dose groups vomited, blood being vomited on all but three occasions.

There was no significant difference in postoperative pallor between the two groups. An inhalation induction was associated with a significantly greater frequency of postoperative pallor than i.v. induction ($P < 0.02$). The method of maintenance made no significant difference.

The dose of premedicant made no significant difference to the frequency of restlessness after operation.

Waking times (table IV)

There was no significant difference between the waking times of those patients premedicated with trimeprazine tartrate 2 mg kg^{-1} and those receiving 4 mg kg^{-1}. Neither group was associated with a significant excess of prolonged recovery. Thirteen patients from the small-dose group and 17 from the large-dose group had not recovered their mental faculties 10 h after premedication, the longest recovery time being 17 h in the small-dose group and 18.25 in the large-dose group. The method of induction and maintenance made no significant difference to the duration of the recovery period.

TABLE IV. *Waking times (from premedication until alert and able to sit)* (h)

	Mean ± SD	Range
Small-dose group ($n = 92$)	6.94 ± 3.31	3.25–17
Halothane maintenance ($n = 77$)	7.17 ± 3.56	
Ether maintenance ($n = 15$)	6.26 ± 1.58	
Large-dose group ($n = 100$)	7.36 ± 3.70	2.5–18.5
Halothane maintenance ($n = 74$)	7.32 ± 3.61	
Ether maintenance ($n = 26$)	7.20 ± 4.00	

Fluid balance (table V)

Twenty-five patients with wet beds were excluded from the fluid output results. These were evenly distributed between the two groups. There was no significant difference in the fluid intake or output of the two groups after operation. All urine specimens contained ketones except the last specimen on the day after operation from 14 patients in the small-dose group and 13 patients in the large-dose group.

TABLE V. *Fluid balance. Means ± SD*

Group	Total fluid intake (ml)	Total urine output (ml)	(ml kg^{-1} h^{-1})
Small-dose	193 ± 114	235 ± 134	0.58 ± 0.17
Large-dose	203 ± 101	241 ± 112	0.57 ± 0.23

DISCUSSION

Trimeprazine tartrate has been used for premedication of children for more than 20 yr, even though it has some undesirable features, notably excessive sedation. We have attempted to quantify the duration of the recovery period after trimeprazine premedication and to assess whether a smaller dose of the drug produces good sedation before operation and suppression of side-effects after operation while leading to less prolonged recovery.

Previous studies have indicated that demeanour in the anaesthetic room and responses to induction are better with a smaller dose of trimeprazine as the less sedated child can more easily cooperate (Gunner and Fox, 1960; Davies and Doughty, 1966). The present investigation showed no significant difference in anaesthetic room demeanour between the two groups.

Postoperative pallor was more frequent after the larger dose of trimeprazine but the difference was not significant. The frequency of pallor was less (20%) in our study than that shown by Davies and Doughty (1966) (56%), who also showed a significant difference in pallor between small and large doses of trimeprazine. Our figures are similar to those of Gordon and Turner (1969), who suggested that the difference between their results and those reported by Davies and Doughty might be explained by excessive pallor being associated with i.v. induction. Our findings refute this suggestion, since 25% of those having an inhalation induction exhibited pallor after operation, compared with only 9% following i.v. induction. The difference in the reported frequency of pallor after operation may be a result of the variation in assessment of this feature.

There was a significant reduction in the frequency of vomiting after operation when the larger dose of trimeprazine was given. Of the patients who vomited, 75% vomited blood on all occasions. Neither dose of trimeprazine was an effective antiemetic when blood was present in the stomach.

Little information has been published on the time taken for children to recover full alertness after operation. Haq and Dundee (1968), comparing diazepam and trimeprazine, mentioned that they recorded the time to return of full mental faculties, but omitted to give any figures. In their study of premedication for day patients, Booker and Chapman (1979) recorded that 11% of children premedicated with morphine and atropine i.m. and 3% of these premedicated with Paedosed (dichloralphenazone + paracetamol) orally were still drowsy 4 h after surgery, but they did not state when these patients became fully alert.

Rapid return to full alertness is important for minor day surgery (Booker and Chapman, 1979) and for children who are required to co-operate during their management after operation or where the facilities for postoperative supervision are less than ideal. It is also important when treating mentally handicapped patients undergoing minor surgical procedures because they may disturb and alarm normal children in the recovery ward. They should return to the familiar environment of their usual ward as soon as they can be adequately cared for as this also helps to reduce their anxieties. Early recovery is needed to allow the resumption of fluid and food intake following minor surgery when prolonged recovery may augment preoperative fluid deficiency (Holden and Maher, 1965), ketosis and hypoglycaemia. A rapid return to alertness is less important when major surgery is performed, as sedation after operation will reduce the discomfort and memory of unpleasant events.

Recovery time is influenced by a number of factors: timing and dosage of premedication, anaesthetic technique, duration of operation and postoperative drugs. The time to return to consciousness following surgery under general anaesthesia is difficult to assess as children may sleep for a long period after operation if left undisturbed and pain free. One of the objects of this study was to find a method of assessing recovery time after operation. Sometimes this is taken as the time of airway ejection and return of laryngeal and pharyngeal reflexes, but this is not always satisfactory and may be misleading. Oral premedication may not have been absorbed before operation in an anxious child, and in the period after operation, after ejection of the airway, the child can become unrousable again as a result of potentiation of postoperative sedation by slowly absorbed premedicant drugs. Patients may lapse into sleep and respiratory depression, after leaving theatre, from this and other causes (Stoddart, 1978). A child should not leave the postoperative ward until the time of maximal effect of any drug administered after operation has passed. In this study, patients were assessed every 15 min and it was felt that the ability to sit unaided for a short period whilst appearing awake and alert and asking or answering relevant questions gave a fairly constant end-point. No patient became depressed or difficult to waken after this time. This method of assessing the recovery gives a longer but safer time for the recovery period.

The similarity of the times taken for recovery and the ranges between the large- and small-dose groups was unexpected. No pharmacokinetic studies have been undertaken with trimeprazine in children (J. Goulton, May & Baker, personal communication), so the similarity between the groups is difficult to explain. The method of induction, maintenance and postoperative drugs made no apparent differences to recovery times. Recovery was prolonged in both groups and was unacceptable in a number of patients. Fourteen per cent of the small-dose group and 17% of the large-dose group required more than 10 h to recover their mental faculties.

The fluid balance results of each group are very similar; this is to be expected if both groups are equally alert. Jenkins, Giesecke and Johnson (1975) suggested that, in adults, a urine output of $1\ \mathrm{ml\,kg^{-1}\,h^{-1}}$ should be aimed for in operative fluid therapy; Davidson (1977) suggested $0.5\text{–}1\ \mathrm{ml\,kg^{-1}\,h^{-1}}$. The example given by Stolley and Schlage (1977) in their study on the normal fluid balance of pre-school children shows that a 24-h urine output as small as $0.5\ \mathrm{ml\,kg^{-1}\,h^{-1}}$ can occur even with normal oral intake. Our mean figure for the urine output from the time of premedication until 8 a.m. the next day was $0.58\ \mathrm{ml\,kg^{-1}\,h^{-1}}$ when only oral fluid was taken. Twenty-two per cent of the small-dose and 24% of the large-dose group had urine outputs less than $0.5\ \mathrm{mg\,kg^{-1}\,h^{-1}}$. Prolonged recovery was not associated with a low urine output as might be expected. The mean urine output for children taking more than 10 h to recover to full alertness was 0.56 $\text{ml kg}^{-1}\,\text{h}^{-1}$. Fluid deficit before and after operation in children undergoing adenotonsillectomy was shown by Holden and Maher (1965), but they gave no figures for urine output after operation. We tried to avoid a fluid deficit before operation by encouraging drinking and giving a glucose drink 4 h before operation. Urine output results suggest that we were successful in about 75% of children. Urinary ketosis was still present in all but 14% of patients on the morning after operation and was unaffected by urine output. A study is in progress to assess whether the ketosis is associated with perioperative hypoglycaemia and whether it can be avoided.

Our study has shown that trimeprazine tartrate either 2 mg kg^{-1} or 4 mg kg^{-1} is effective for premedication of children aged 2–10 yr with regard to demeanour before operation and suppression of side-effects after operation. The frequency of prolonged recovery of full alertness with both doses was such as to question their suitability for routine use for day surgery or when prolonged sedation is not desirable after operation.

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LE TARTRATE DE TRIMEPRAZINE EN TANT QUE MEDICATION PREOPERATOIRE POUR LES ENFANTS

RESUME

On a effectué une étude à double inconnue pour comparer les effets d'une médication préopératoire, administrée par voie buccale, à raison de 2 mg kg^{-1}, ou de 4 mg kg^{-1} de tartrate de triméprazine, sur 192 enfants devant subir une amygdalectomie. On a étudié leur comportement avant l'opération et les effets secondaires après l'intervention chirurgicale, de même que les temps nécessaires à leur reprise de conscience et l'équilibre des fluides. Leur comportement dans la salle d'anesthésie et leur nervosité après l'intervention chirurgicale n'ont pas été affectés par la dose administrée. Il y a eu moins de vomissements avec la dose de 4 mg kg^{-1} qu'avec celle de 2 mg kg^{-1}. On a fréquemment constaté des temps de reprise de conscience prolongés dans les deux groupes, 14% du groupe ayant reçu la faible dose et 17% du groupe ayant reçu la dose forte ont pris plus de 10 h pour retrouver toutes leurs facultés mentales. L'équilibre des fluides n'a pas été affecté par la dose et la reprise de conscience prolongée n'a pas entraîné de réduction de la production d'urine. Le tartrate de triméprazine n'est pas recommandé comme médication préopératoire lorsqu'on souhaite avoir une reprise de conscience rapide.

VORBEHANDLUNG VON KINDERN MIT TRIMEPRAZINTARTRAT

ZUSAMMENFASSUNG

Ein Doppelblindversuch wurde durchgeführt, um die Wirkungen von Trimeprazintartrat (2 mg kg^{-1} oder 4 mg kg^{-1}) mit Atropin 0,03 mg kg^{-1} als orale Vorbehandlung von Kindern (192) für Tonsillektomie zu vergleichen. Studiert wurden das Aussehen vor der Operation, Nebenerscheinungen nach der Operation, Erholungszeiten und Flüssigkeitsgleichgewicht. Das Verhalten im Narkosezimmer und postoperative Ruhelosigkeit wurden von der verabreichten Dosis nicht beeinflusst. Bei 4 mg kg^{-1} gab es weniger Erbrechen als bei 2 mg kg^{-1}. Verlängerte Erholungszeiten ergaben sich häufig in beiden Gruppen, wobei 14% aus der Gruppe mit kleiner und 17% aus der Gruppe mit hoher Dosis länger als 10 Stunden benötigten, ihre normalen geistigen Fähigkeiten wieder herzustellen. Das Flüssigkeitsgleichgewicht blieb unberührt, und die verlängerte Erholungzeit führte nicht zu einer reduzierten Harnabgebe. Trimeprazintartrat wird als routinemässige Vorbehandlung nicht empfohlen, wenn rasche Erholung erforderlich ist.

PREMEDICACION DE LOS NIÑOS CON TARTRATO DE TRIMEPRAZINA

SUMMARIO

Se llevó a cabo una prueba de doble anonimato para comparar los efectos de 2 mg kg^{-1} o de 4 mg kg^{-1} de tartrato de trimeprazina con 0,03 mg kg^{-1} de atropina para la premedicación oral de 192 niños sometidos a tonsillectomía. Se estudiaron la conducta antes de la operación y los efectos secundarios después de ésta, los tiempos de recuperación y el equilibrio de los flúidos. La conducta en el teatro de operaciones y la inquietud después de la intervención quirúrjica vinieron afectados por la dosis dada. Tuvo lugar una menor cantidad de vómitos asociados con 4 mg kg^{-1} en comparación con 2 mg kg^{-1}. En ambos grupos tuvieron lugar, con frecuencia, prolongados periodos de recuperación, 14% para el grupo de la dosis menor y 17% en el de la dosis mayor, siendo más de 10 minutos necesarios para la total recuperación de sus facultades mentales. El equilibrio de los flúidos no quedó afectado por la dosis y la prolongada recuperación no tuvo como consecuencia una reducción en la producción de orina. No se recomienda el tartrato de trimeprazina para las premedicaciones rutinarias cuando es necesaria una temprana recuperación.

Br. J. Anaesth. (1981), 53, 827

ANAESTHESIA WITH FLUNITRAZEPAM AND KETAMINE

I. FREUCHEN, J. ØSTERGAARD AND B. OHRT MIKKELSEN

SUMMARY

A randomized study of 96 women undergoing hysterectomy was used to compare two anaesthetic techniques: flunitrazepam, ketamine and nitrous oxide in oxygen; and pethidine, thiopentone, nitrous oxide in oxygen and halothane. The techniques exerted small, but significantly different influences on heart rate and arterial pressure. Significantly more patients complained of nausea and vomiting on awakening after inhalation anaesthesia. Amnesia after operation lasted significantly longer after flunitrazepam combined with ketamine and nitrous oxide in oxygen.

Flunitrazepam administered i.v. affects the cardiovascular system minimally and has a slight and transitory depressant effect on the respiratory centre (Freuchen and Østergaard, 1974). In a double-blind trial comparing the drug with enibomal as a sedative before anaesthesia Freuchen, Østergaard and Ohrt Mikkelsen (1976) noted short-lasting respiratory depression with both drugs. However, the effect of flunitrazepam on the circulation was minimal.

The benzodiazepines can prevent or decrease the psychotomimetic side-effects observed during awakening from ketamine anaesthesia in adults. Knoche, Traub and Dick (1978) compared diazepam, flunitrazepam and placebo in this context and found the amnesic and anxiolytic properties of flunitrazepam and its minimal effect on the circulation advantageous. In a double-blind study, Freuchen and colleagues (1976) found that the simultaneous injection of flunitrazepam and ketamine decreased significantly the frequency of dreams, confusion and motor restlessness during awakening.

Chodoff and Stella (1966) used a continuous infusion i.v. in an attempt to decrease the adverse effects of ketamine during awakening. Since then this method of administration has been used extensively.

PATIENTS AND METHODS

Ninety-six women undergoing hysterectomy participated in the study. The trial was designed in accordance with the Declaration of Helsinki and the patients were allocated randomly to one of two different methods of anaesthe isa. Method I—ataranalgesia: Flunitrazepam 2 mg was given orally on the night before the operation. Flunitrazepam 1 mg was administered i.m. 30–60 min before surgery. Atropine 0.5 mg i.v. was given and anaesthesia was induced with flunitrazepam 2 mg as a slow i.v. injection (1 mg = 1 ml per 30 s) and ketamine 1 mg kg^{-1}. Suxamethonium was administered i.v., the trachea intubated and inhalation anaesthesia initiated with 60% nitrous oxide in oxygen. Alcuronium 10 mg i.v. was given initially and supplemented with 2.5 mg when necessary. Ketamine 0.1% in 5% glucose was infused continuously using the Injectomat 50 (Fresenius) injection pump, the rate of infusion being adjusted as necessary, depending on the response of the individual patient.

Method II — inhalation anaesthesia: Nitrazepam 5 mg was given orally on the night before the operation. Pethidine 50–100 mg was administered i.v. 30–60 min before the operation. At induction of anaesthesia atropine 0.5 mg and thiopentone 250–500 mg were given i.v. Suxamethonium was administered i.v., the trachea intubated and inhalation anaesthesia (halothane in 60% nitrous oxide in oxygen) was initiated. Suxamethonium was infused continuously i.v.

Arterial pressure and heart rate were measured every 5 min before and during anaesthesia: any evidence of cardiac arrhythmia (e.c.g.) was recorded. After the operation, the patients were observed in the recovery room until the following morning. Nausea and vomiting, restlessness, changes in mental state and the degree of amnesia were noted. The degree of amnesia was recorded by asking the patients, before leaving the recovery

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room, if arriving at the operating theatre or anything about the operation could be remembered and the first memory of regaining consciousness.

The statistical analysis comprised both parametric and non-parametric methods. Intra-patient comparisons were made with the paired t-test and comparisons between the two methods performed with the G-test, χ^2-test, the Mann–Whitney rank sum test and parametric two-factor (treatments and time) analysis of variance with replication on the factor time.

RESULTS

The median age of the patients was 44 yr (range 29–75 yr). Median height was 162 cm (range 148–180 cm) and median weight was 62 kg (range 46–90 kg). Sixteen patients had one or more risk factors such as cardiovascular disease, allergy, diabetes etc. Before operation, 91 patients were judged to be in good general condition and five patients in a moderate condition. The median duration of the operation was 92 min (range 45–230 min). The two groups did not exhibit statistically significant differences as regards these criteria or their initial heart rates and arterial pressures.

The influence of premedication on the patients' condition before operation did not differ in the two groups ($P > 0.10$). Seven patients were somnolent, 73 were calm and 16 were nervous.

During ataranalgesia (method I), the median amount of additional ketamine was 103 mg (range 40–267 mg); supplements from 1 to 4 mg of flunitrazepam were given to seven patients. During inhalation anaesthesia (method II), supplements of pethidine 15–50 mg were given to 29 patients and supplements of thiopentone 50–200 mg to six patients.

Irrespective of therapy there was a systematic variation with time in heart rate ($P < 0.01$) (fig. 1). There were no significant overall differences between the two methods ($P \ngtr 0.10$) but the time-courses were not identical. This was substantiated by the analyses of variance which demonstrated a statistically significant interaction between treatment and time ($P < 0.05$). Treatments were accordingly different even though this was evident only when the changes in heart rate over time were taken into account.

Systolic and diastolic arterial pressures showed significant variations during anaesthesia irrespective of the method of anaesthesia ($P < 0.01$) (fig. 2). Systolic arterial pressure showed a significant difference between the two methods irrespective of time ($P < 0.01$), but this was not so with diastolic arterial pressure ($P > 0.10$). For systolic and diastolic arterial pressures the time-courses were not identical in the two treatments. This was substantiated by the analysis of variance which demonstrated a statistically significant interaction between treatment and time ($P < 0.01$)

Arrhythmia during anaesthesia was observed in four patients under ataranalgesia and in six patients under inhalation anaesthesia. With inhalation anaesthesia a significantly greater number of patients (46%) had complications after operation than with ataranalgesia (17%)

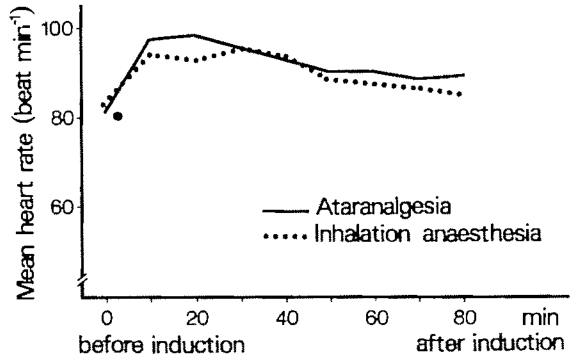

FIG. 1. Influence of ataranalgesia and inhalation anaesthesia on heart rate.

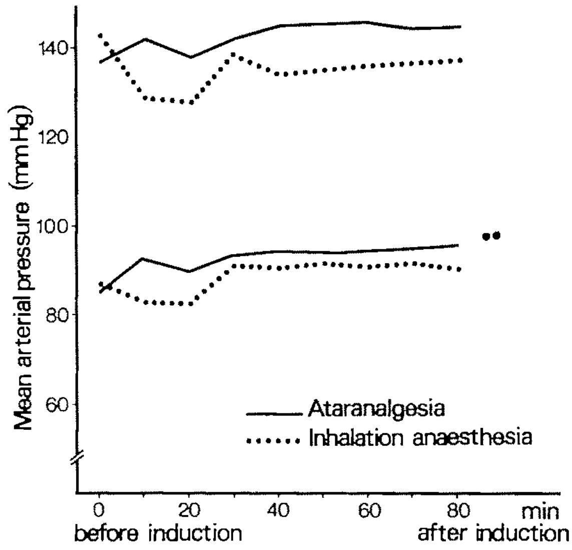

FIG. 2. Changes in mean systolic and diastolic arterial pressures during ataranalgesia and inhalation anaesthesia.

($P < 0.005$) (table I). The frequency of nausea or vomiting, or both, after inhalation anaesthesia was not significantly different between patients who had supplementary pethidine and those who had not. Five patients receiving ataranalgesia and three patients undergoing inhalation anaesthesia were amnesic about their arrival in the operating theatre. No patient remembered the operation. The duration of amnesia after operation was significantly longer following ataranalgesia (median 117 min, range 0–480 min) than after inhalation anaesthesia (median 80 min, range 15–330 min) ($P < 0.05$).

TABLE I. *Patients with complications after operation.* * *One patient had two complaints;* † *five patients had two complaints and one had three complaints*

Complication	Ataranalgesia ($n = 46$)	Inhalation anaesthesia ($n = 50$)
Nausea	6	21
Vomiting	2	8
Restlessness		1
Mental disturbances	1	
Total	8* (17%)	23† (46%)

DISCUSSION

The designation "ataranalgesia" for the combination of flunitrazepam and ketamine was introduced by De Castro (1973). We have used this term although we think that "ataranaesthesia" would be more appropriate.

The rate of elimination of flunitrazepam is slow, the half-life being 3–5 h for the α phase and about 19 h for the β phase. During breakdown, three major metabolites are formed, all with a half-life longer than that of the parent substance (Wendt, 1976) and consequently, accumulation may occur. These metabolites are pharmacologically less active and presumably do not influence the clinical effect of flunitrazepam. Excretion takes place through the kidneys. The therapeutic dose is 1–2 mg, but after ingestion of up to 50 mg only deep sleep was observed (Lingjaerde, 1977). If used as a sedative in the evening, hangover and a decrease in functional ability may occasionally be observed, presumably because of the long half-life. With administration i.v. as an anaesthetic, these effects are of less importance and the pronounced amnesia is advantageous, since anything experienced at the commencement of anaesthesia and in the period after anaesthesia becomes blurred.

Radaković (1976) described the beneficial anxiolytic effect of flunitrazepam at the induction of anaesthesia. About 2 min after an initial injection of 0.25–0.5 mg i.v. on arrival in the anaesthetic room or operating theatre, anxiety-dependent inhibitions disappeared, the state of mind became optimistic and speech became slow, but free. The patients co-operated well and did not object to manual ventilation. When asked to do so, the patient put out his tongue and agreed to direct laryngoscopy so that the glottis could be examined at rest and during phonation. During this procedure respiration was calm and the glottic reflexes preserved without laryngospasm.

Ketamine (half-life 11 min for the α phase and about 80 min for the β phase) is broken down rapidly in the liver to form four metabolites which are excreted through the kidneys (98%) and in the faeces (2%) (Idvall et al., 1979). Because of the rapid distribution, the anaesthetic effect lasts from 10 to 15 min and, consequently, supplements of half the induction dose have to be given at these intervals. The plasma concentration must be approximately 8–10 μmol litre^{-1} to produce anaesthesia (Idvall et al., 1979). Using a continuous i.v. infusion, it is possible to achieve this concentration and to avoid an overdose which might cause unwanted side-effects.

Occasionally the i.v. infusion is called "micro-mini drip technique" (Hatano et al., 1976), since a special drip chamber is used which supplied 50 drops per ml (Buretrol 2C0133 Baxter). Reliable continuous infusion is often ensured by means of an infusion pump coupled to the infusion set.

Albin and Figallo (1977) titrated the anaesthetic plasma concentration by excluding nystagmus, changes in arterial pressure and response to the surgical intervention and found that, compared with the intermittent injection technique, they used less than half the quantity of ketamine. Hatano, Nishiwada and Matsumura (1978) administered ketamine by infusion and observed safe and smooth induction and maintenance of anaesthesia with an awakening almost completely without psychotomimetic reactions. By administering ketamine by infusion, Hatano and colleagues (1976) found that, in contrast to bolus injection, there were less pronounced effects on the circulation and respiration, minimal mental and motor disturbances after operation and good amnesia.

The present study has proved that flunitrazepam–ketamine anaesthesia is a satisfactory alternative to barbiturate–halothane anaesthesia used widely for major surgery.

It should be possible to exploit the amnesic and anxiolytic effects of flunitrazepam in combination with other analgesics such as fentanyl. Unwanted contamination by gaseous anaesthetics present in operating theatres can be avoided by using i.v. anaesthetics and the possible risk of undesirable effects of halothane on the liver eliminated.

ACKNOWLEDGEMENT

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ANESTHESIE A L'AIDE DE FLUNITRAZEPAM ET DE KETAMINE

RESUME

On s'est basé sur les résultats d'une étude effectuée au hasard sur 96 femmes subissant une hystérectomie pour comparer deux techniques d'anesthésie: flunitrazépam, kétamine et protoxyde d'azote dans l'oxygène et, péthidine, thiopentone, protoxyde d'azote dans l'oxygène et halothane. Les techniques utilisées ont exercé de faibles influences, bien que significativement différentes, sur la fréquence cardiaque et la pression artérielle. Un plus grand nombre de patients s'est plaint de nausées et de vomissements au moment du réveil de l'anesthésie par inhalation. L'amnésie, après l'opération, a duré plus longtemps après le flunitrazépam allié à la kétamine et au protoxyde d'azote dans l'oxygène.

NARKOSE MIT FLUNITRAZEPAM UND MIT KETAMIN

ZUSAMMENFASSUNG

Eine wahllose Studie an 96 Hysterektomie-Patientinnen wurde zum Vergleich zweier Narkosemethoden verwendet: Flunitrazepam, Ketamin und Stickoxyd in Sauerstoff einerseits, Pethidin, Thiopenton, Stickoxyd in Sauerstoff und Halothan andererseits. Diese Methoden hatten geringe, aber deutlich verschiedene Auswirkungen auf die Herztätigkeit und den arteriellen Druck. Wesentlich mehr Patientinnen klagten über Übelkeit und Erbrechen nach Erwachen aus der Narkose. Bei Flunitrazepam und Ketamin mit Stickoxyd in Sauerstoff dauerte die postoperative Amnesie wesentlich länger.

ANESTESIA CON FLUNITRAZEPAM Y KETAMINA

SUMARIO

Se usó estudio aleatorizado de 96 mujeres sometidas a histerectomía para comparar dos técnicas anestésicas: flunitrazepam, ketamina y óxido nitroso en oxígeno; y petidina, tiopentona, óxido nitroso en oxigeno y halotano. Las técnicas ejercieron pequeñas, pero significativamente diferentes, influencias sobre el ritmo cardiaco y la presión arterial. Lo significativo fue que hubo más pacientes que se quejaron de náuseas y vómitos al despertarse después de haber inhalado la anestesia. La amnesia posoperativa duró significativamente más después de la combinación de flunitrazepam con ketamina y óxido nitroso en oxígeno.

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CLINICAL EVALUATION OF DIAZEPAM FOR RELIEF OF POSTOPERATIVE PAIN

P. N. SINGH, P. SHARMA, P. K. GUPTA AND K. PANDEY

SUMMARY

Morphine 10 mg or diazepam 10 mg or a mixture of morphine 5 mg and diazepam 5 mg were given i.m. to three groups of 35 patients for relief of pain in the period immediately after operation. The patients had undergone upper abdominal operation for which a uniform regime of premedication and anaesthesia had been used. Pain was assessed by an observer before and after treatment and by the subjects, using a five-point scoring scheme. The pain scores before treatment and at 30-, 60-, 90- and 120-min intervals after treatment were compared by Ridit analysis. All three treatments produced significant relief, but the relief after diazepam alone was not as long-lasting as after the other two treatments. No clinically significant cardiovascular or respiratory complications occurred. Diazepam alone was associated with significantly more restlessness and morphine alone was associated with significantly more sickness. The combination of morphine and diazepam was considered to be the treatment of choice.

In an uncontrolled study Bruce (1968) compared the pain-relieving actions of diazepam and morphine in patients who had undergone surgical operations of varying severity and formed the opinion that the analgesic action of the two drugs was comparable. Hollis (1968), Kyles (1968) and Moore (1968) also observed that the use of diazepam reduced the requirement of narcotic analgesics in the period after operation, but the claim of an analgesic action of diazepam has not been supported by others (McClish, 1966; Haslett, 1968; Dundee and Wyant, 1974). No clinical study evaluating the pain-relieving properties of diazepam has been reported. This double-blind study was undertaken to compare diazepam and morphine.

METHODS

Subjects

One hundred and five patients complaining of pain following upper abdominal operations were studied. All patients weighed 45–60 kg, were aged between 20 and 60 yr, and were of physical status grades 1 and 2 of the American Society of Anesthesiologists' classification. None had received an analgesic drug before operation and all were considered to be capable of co-operating in the assessment of pain.

Anaesthetic technique

Atropine 0.6 mg and promethazine 25 mg were given i.m. 45–60 min before operation. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and tracheal intubation facilitated by suxamethonium 50–75 mg. Anaesthesia was maintained with nitrous oxide and oxygen 3 : 1.5 litre min^{-1} in a circle system with spill-over and a non-depolarizing neuromuscular blocking drug was given to permit controlled ventilation of the lungs. At the end of operation, its action was antagonized by neostigmine 1–2 mg preceded by atropine sulphate 0.6–1.2 mg. The duration of anaesthesia varied between 75 and 150 min.

Assessment and relief of postoperative pain

When patients had become fully conscious in the recovery ward, the severity of pain was estimated by both the patient and the observer (P. N. S.) according to the method described by Loan, Morrison and Dundee (1968). This rates pain on a five-point scale (table I) and uses both the patient's and trained observer's estimate of severity. Only those subjects whose initial pain score was 3 or 4 were included in the study.

Patients were allocated at random to receive one of three treatments which was given i.m. by another investigator (so that its nature would not

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TABLE I. *Scoring scheme for pain severity*

Patient's estimate	Score	Observer's estimate
Very severe	4	Patient writhing, sweating, distressed
Severe	3	Strained facial expression only
Moderate	2	Patient lying still, eyes open or closed, and avoiding movements
Mild	1	Patient drowsy or sleeping with no tendency to avoid movements
No pain	0	No discomfort, completely at ease moving and coughing comfortably

be known to the observer): group I = morphine 10 mg; group II = diazepam 10 mg; group III = morphine 5 mg + diazepam 5 mg.

The severity of pain was estimated before and at 30-, 60-, 90- and 120-min intervals after treatment.

Arterial pressure, heart rate and respiratory rate were also recorded at the same time as the pain scores. Other observations included the occurrence of restlessness, sleep, vomiting and pain at the site of injection of the trial drugs.

Methods of statistical analysis

The significance of changes in the mean values of the mean arterial pressure (Jennings, 1964), heart rate and respiratory rate was assessed using the paired *t* test. The mean pain severity scores before and after treatment were compared using Ridit analysis (Bross, 1958; Dundee, Moore and Nicholl, 1962; Pandey, Ratra and Badola, 1967). The numbers of subjects with and without a particular characteristic (table V) were charted as 2 × 2 contingency tables (Bailey, 1959).

RESULTS

Three groups of 35 fit patients were broadly comparable with respect to mean age, body weight, sex distribution and frequency of ASA risk grades (table II).

TABLE II. *Mean age (± SEM), mean body weight (± SEM), sex and physical status in the three treatment groups*

	Treatment group		
	Morphine 10 mg	Diazepam 10 mg	Morphine 5 mg + diazepam 5 mg
Mean age (yr)	39 ± 1.5	40 ± 1.5	38 ± 1.7
Mean body weight (kg)	51 ± 0.7	49 ± 0.8	50 ± 0.7
Males	16	14	13
ASA grade 1	26	25	28

Pain relief

Table III illustrates the average initial pain scores in the three groups with the mean scores at 30-, 60-, 90- and 120-min intervals after the treatments.

A within-group comparison of the mean ridits at various times after treatment with the mean ridits before treatment (the identified distribution) is illustrated in figure 1. All three treatments were associated with a significant reduction in mean pain score as revealed by the lack of overlap between the 95% confidence limits of the post- and pre-treatment mean ridit.

A between-group comparison of the pain scores was also made. The mean ridits in the morphine-treated groups at each time of assessment served as

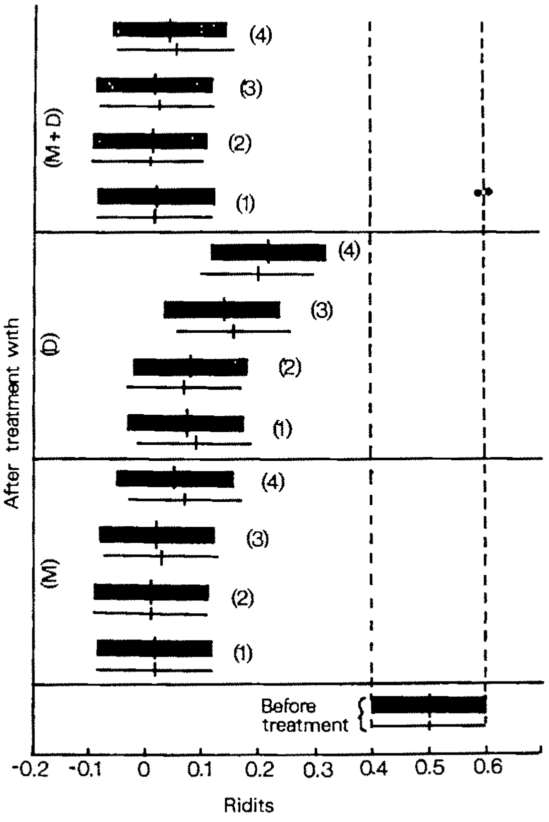

FIG. 1. Mean pain score ridits (with 95% confidence limits) based on the patients' (thin bars) and observers' (thick bars) estimates at 30 (1), 60 (2), 90 (3) and 120 (4) min after treatment. Mean pain score ridits and their 95% limits observed before giving the treatments form the identified distribution and these, being identical in each group, are represented by the single pair of thin and thick bars marked "Before treatment". (M), (D) and (D + M) indicate treatments with morphine, diazepam, and diazepam + morphine, respectively.

TABLE III. *Mean pain scores before and at various time intervals after the trial drugs. Scores: P = patient estimates; O = observer estimates*

Time of estimating scores	Treatment group					
	Morphine 10 mg		Diazepam 10 mg		Morphine 5 mg + diazepam 5 mg	
	P	O	P	O	P	O
Before treatment	3.8	3.7	3.8	3.7	3.8	3.7
30 min	2.0	1.9	2.4	2.2	1.9	1.9
60 min	1.7	1.6	2.4	2.3	1.8	1.7
90 min	2.0	1.9	2.8	2.7	2.0	1.9
120 min	2.3	2.1	3.1	3.0	2.2	2.1

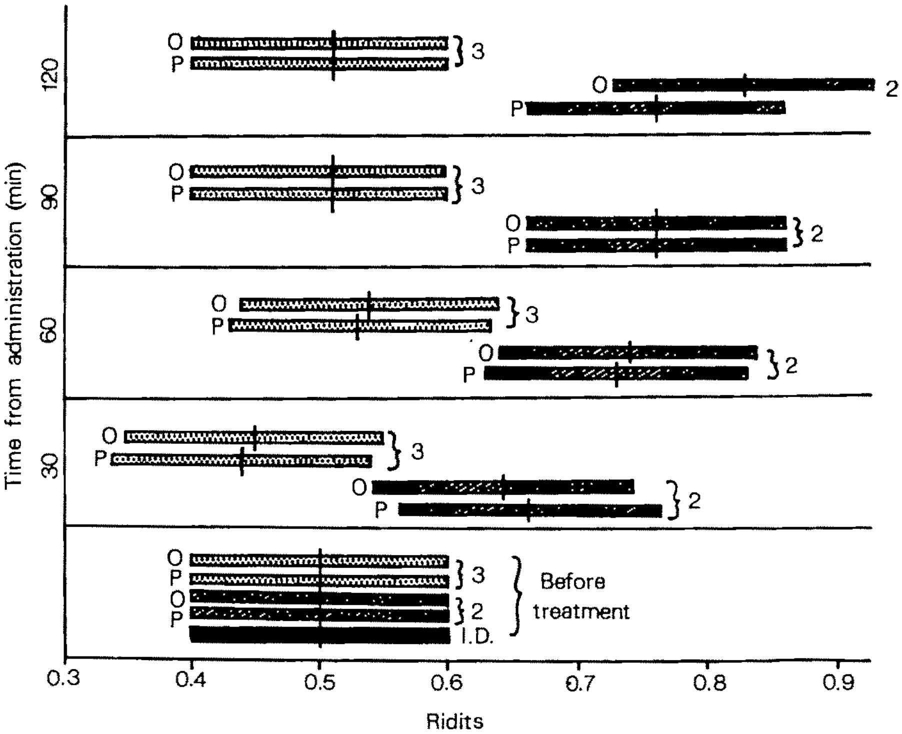

FIG. 2. Comparison of mean pain score ridits in the three treatment groups, before and at 30-, 60-, 90- and 120-min after the treatments. P = ridits based on patients' estimate. O = ridits based on observers' estimate. The mean ridits (with 95% confidence limits) in the diazepam-treated group are shown by scored bars (marked 2); stippled bars (marked 3) represent the diazepam + morphine treated group. Mean ridits (with 95% confidence limits) in the morphine-treated group at each time form the identified distribution. The identified distributions, being identical, are represented by the thickly stippled bar at the bottom. Overlap between the 95% confidence limits of the mean ridits in the morphine + diazepam and morphine-treated groups indicates lack of any significant difference in the efficacy of the two treatments. Diazepam alone is associated with significantly less pain relief at 60-, 90- and 120-min intervals (as indicated by a lack of overlap between the 95% confidence limits of the mean ridits in this group and those in the identified group).

the identified distributions and were compared with the corresponding mean ridits in the other two groups (fig. 2). Using the method of comparison, the efficacy of the three treatments was indistinguishable 30 min after drug administration. Thereafter, diazepam alone proved to be significantly less effective in relieving pain when compared with morphine alone or the combination of morphine and diazepam.

These conclusions applied irrespective of the ridit analysis being based on the patient's or the observer's estimate of pain severity.

Cardiovascular and respiratory effects

A significant reduction in the mean of mean arterial pressure and mean respiratory rate was associated with each of the three treatments (table IV). However, the decrease in the mean of the mean arterial pressure observed after diazepam was of less duration than those after the other two treatments.

TABLE IV. *Mean changes in mean arterial pressure and respiratory rate after the three treatments. * Changes significant* (P<0.05). *I = morphine 10 mg; II =* diazepam 10 mg; III *= morphine 5 mg + diazepam 5 mg*

	Treatment group	Time after administration (min)			
		30	60	90	120
Change in mean arterial pressure	I	−7±1.9*	−10±1.6*	−9±1.6*	−8.0±1.8*
	II	−5±1.3*	−4±1.3*	−3±1.3*	−0.3±0.9
	III	−7±1.8*	−10±1.7*	−8±1.7*	−7.0±1.6*
Change in respiratory rate	I	−6±0.6*	−8±0.6*	−7±0.6*	−6.0±0.6*
	II	−2±0.5*	−3±0.5*	−2±0.5*	−1.0±0.4*
	III	−5±0.6*	−6±0.6*	−6±0.6*	−5.0±0.6*

Other observations

Table V indicates the number of patients who remained awake or restless, felt sick or complained of pain at the injection site. Treatment with diazepam alone was associated with a significantly greater frequency of restlessness and failure to sleep. Morphine alone was followed by a significantly greater frequency of sickness, but was not associated with persistent pain at the injection site.

TABLE V. *Other observations in patients in each group. * Significantly greater than in groups I and III* (P<0.05); *† Significantly greater than in groups II and III* (P<0.05). *Exact probabilities of obtaining the 2×2 contingency tables were calculated and then shown as more or less than 0.05, the critical level*

	Treatment group		
	Morphine 10 mg	Diazepam 10 mg	Morphine 5 mg + diazepam 5 mg
Awake and restless	3	11*	3
Awake but not restless	3	7	3
Sick	9†	2	2
Pain at injection site	0†	5	2

DISCUSSION

Using subjective and observer pain scores as a means of assessing analgesia we found that significant pain relief occurred in the patients who had received diazepam, but it was not as sustained as after morphine or after a combination of morphine and diazepam in smaller doses.

The precise mechanism of the "pain relieving" action of diazepam is difficult to explain and, as suggested by Brown (1968), its sedative and tranquillizing properties may, to a large extent, be responsible for our findings. The sedative action of morphine is thought to contribute to analgesia. The relative brevity of the "analgesic" action of diazepam, as compared with that of morphine, is reminiscent of the placebo response, where psychological factors play a major part. Another contributory factor may be the central muscle relaxant action of diazepam since muscle spasm is an invariable component of the pain following abdominal incisions.

We do not know the nature of the "true analgesia" component of narcotic analgesics, and the "totality of behavioural change" still remains the only yardstick for measurement of analgesic action. This study has provided evidence of a strong interaction between morphine and diazepam.

Our results show that, in the doses used, morphine alone was superior to the morphine–diazepam combination as far as intensity of analgesia is concerned, but the use of the combination was associated with significantly less sickness. The cardiovascular and respiratory effects of the combination and morphine alone were identical. The frequency of pain at the injection site was low when the combination was used and should not detract from its value (Marks, 1967; Eisenberg, Taub and Burana, 1974). Lawrence (1966) has suggested that the use of drugs to relieve pain should not be guided solely by their efficacy, but also by their propensity to produce wanted side actions.

The value of tranquillizers as adjuvants in the relief of chronic pain is well known and they have an established place in treatment. This is the first report of their use in the treatment of pain following surgery. Undoubtedly this subject is worthy of further investigation. It must be emphasized that our encouraging results apply to 5–10-mg doses of diazepam; if these are increased then the prolonged soporific effect of the benzodiazepine might be a disadvantage. Furthermore, the preoperative use of diazepam 10 mg with "normal" doses of analgesic has resulted in undue cardiovascular depression (Dundee et al., 1970).

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EVALUATION CLINIQUE DU DIAZEPAM POUR LE SOULAGEMENT DES DOULEURS POST-OPERATOIRES

RESUME

On a administré par voie intramusculaire à trois groupes de 35 patients: 10 mg de morphine, ou 10 mg de diazépam, ou un mélange de 5 mg de morphine et de 5 mg de diazépam pour soulager la douleur au cours de la période qui a immédiatement suivi l'intervention chirurgicale. Les patients avaient subi une opération à la partie haute de l'abdomen, pour laquelle on avait utilisé un régime uniforme de médication préopératoire et d'anesthésie. La douleur a été évaluée par un observateur, avant et après le traitement, et par les sujets, à l'aide d'un système de notation à cinq points. Les points relatifs à la douleur avant le traitement et à des intervalles de 30 min, 60 min, 90 min et 120 min après le traitement ont été comparés par analyse Ridit. Ces trois traitements ont chacun produit un soulagement significatif, mais le soulagement après le diazépam seul n'a pas été d'aussi longe durée qu'après les deux autres traitements. Il ne s'est produit aucune complication respiratoire ou cardiovasculaire ayant une importance clinique. Le diazépam seul a été associé à une nervosité plus marquée et la morphine seule à davantage de nausées. La combinaison de morphine et de diazépam a été considérée comme étant un traitement de choix.

KLINISCHE BEURTEILUNG VON DIAZEPAM ALS POSTOPERATIVES SCHMERZLINDERUNGSMITTEL

ZUSAMMENFASSUNG

Zehn mg Morphium oder Diazepam, bezw. eine Mischung aus je 5 mg beider Drogen wurde intramuskulär als Schmerzlinderungsmittel unmittelbar nach Operationen an drei Gruppen von 35 Patienten verabreicht. Die Patienten hatten Eingriffe im oberen Unterleib hinter sich, mit einheitlicher Vorbehandlung und Narkose. Die Schmerzen wurden vor und nach der Behandlung von einem Beobachter und von den Patienten selbst eingeschätzt, mit Hilfe einer Fünf-Punkte-Skala. Die Schmerz-Werte vor der Behandlung

und in Abständen von 30, 60, 90 und 120 min nach der Behandlung wurden durch Ridit-Analyse verglichen. Alle drei Behandlungsweisen erzielten signifikante Schmerzlinderung, doch war die Wirkung mit Diazepam allein nicht so lang andauernd als mit den beiden anderen Behandlungsweisen. Klinisch signifikante kardiovaskuläre oder respiratorische Komplikationen traten nicht auf. Diazepam allein bewirkte wesentlich erhöhte Ruhelosigkeit, Morphium allein wesentlich mehr Übelkeit. Die Kombination von Morphium und Diazepam wird als beste Behandlungsweise betrachtet.

EVALUACION CLINICA DEL DIAZEPAM PARA EL ALIVIO DEL DOLOR POSOPERATIVO

SUMARIO

Se administró por vía intramuscular 10 mg de morfina, ó 10 mg de diazepam, o una mezcla de 5 mg de morfina y 5 mg de diazepam, a tres grupos de 35 pacientes, para aliviar el dolor inmediatamente después de la operación. A los pacientes se les sometió a operación quirúrjica de la parte superior del abdomen, para lo que se usó un régimen uniforme de premedicación y de anestesia. El dolor se evaluó mediante un observador antes y después del tratamiento, así como por parte de los sujetos, utilizando para esto un plan de puntuación de 5 puntos. La puntuación de dolor antes del tratamiento y a intervalos de 30, 60, 90 y 120 min después de dicho tratamiento se comparó con el análisis de Ridit. Los tres tratamientos produjeron un alivio significativo, pero el producido por la administración exclusiva de diazepam no fue de tanta duración como el alivio conseguido después de los otros dos tratamientos. No tuvieron lugar complicaciones cardiovasculares ni respiratorias de significación clínica. Sólo el diazepam vino asociado con un significativo aumento de la inquietud y sólo la morfina vino asociada con un grado significativo de aumento de la enfermedad. Se consideró que la combinación de diazepam y morfina es el tratamiento opcional.

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CHANGES IN PLASMA CATECHOLAMINE CONCENTRATIONS DURING ENDOTRACHEAL INTUBATION

W. J. RUSSELL, R. G. MORRIS, D. B. FREWIN AND S. E. DREW

SUMMARY

The changes in arterial pressure and arterial concentrations of noradrenaline, adrenaline and dopamine were monitored in 16 patients undergoing endotracheal intubation. Significant increases in mean arterial pressure and plasma noradrenaline were noted. The increases in arterial pressure were associated with increases in noradrenaline concentrations. Adrenaline and dopamine concentrations did not change significantly following intubation. The results suggest a predominantly sympathetic response during intubation and the need for prophylaxis in patients at risk.

The introduction of a foreign body into the trachea is almost always associated with cardiovascular disturbances (Siedlecki, 1975). These include a significant increase in arterial pressure and ventricular premature beats. Although these cardiovascular manifestations during anaesthesia are recognized, there is little documented evidence on the mechanisms of their production. Alpha- and beta-adrenergic blockers have been used to minimize these changes and successful results have been reported following ganglion blockade (Siedlecki, 1975).

The basis for adrenergic blockade is the assumption that increases in plasma catecholamine concentrations could contribute to cardiovascular changes during intubation. This has not been validated; few studies on plasma catecholamine concentrations during surgery have been reported (Butler et al., 1977). The present study examined changes in plasma catecholamine concentrations during intubation to determine if an increase occurred, and if one specific catecholamine might predominate.

METHODS

Sixteen patients aged 25–80 yr undergoing elective surgery were studied. Each received premedication, usually morphine and atropine. Arterial pressure was recorded from a heparinized cannula placed in a radial artery and blood for catecholamine estimations was obtained through this line. Anaesthesia was induced with a sleep-dose of thiopentone i.v. Pancuronium was administered and the lungs ventilated with nitrous oxide in oxygen.

The study was conducted in two stages. Samples from the first eight patients were taken before induction of anaesthesia and at 1, 5 and 10 min after tracheal intubation. The results indicated that a further sample was necessary after induction of anaesthesia, but before intubation, to separate any effects of premedication and anaesthetic agents from the effects of intubation. This further sample was taken in the second group of eight patients; the other sampling sequence remained unchanged. The blood was collected into chilled heparinized tubes (lithium heparin 125 u./10 ml^{-1}) which contained glutathione 5 mmol litre^{-1}. The samples were centrifuged and the plasma separated from cells. Samples were then deproteinized with an equal volume of perchloric acid 0.6 mol litre^{-1} containing EGTA 10 mmol litre^{-1} and magnesium chloride 1 mmol litre^{-1}, centrifuged again and the supernatant stored at −20 °C.

Assay of catecholamines

Catecholamines (noradrenaline, adrenaline and dopamine) were estimated using a modification of the radioenzymatic method of Da Prada and Zürcher (1976). Each of the catecholamines is converted to the respective O-methylated product by catechol-O-methyltransferase (COMT) in the presence of ^{3}H-S-adenosyl methionine. These

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products are then extracted, purified, and finally separated by thin-layer chromatography, and radioactivity determined and compared with standards. This assay has been validated in our laboratory by appropriate recovery procedures.

RESULTS

Table I and figure 1 show the changes in mean arterial pressure and plasma catecholamine concentrations which occurred following induction of anaesthesia and endotracheal intubation. As the values before anaesthesia for stages 1 and 2 of the study were similar, the results obtained from all 16 patients were grouped together. A significant decrease in arterial pressure was observed following induction of anaesthesia. The mean values for adrenaline and noradrenaline also decreased, but the changes were not statistically significant.

Significant increases in mean arterial pressure and noradrenaline concentration were noted 1 min after intubation, and these changes gradually regressed with time. Changes in adrenaline and dopamine concentrations over the same time period were not statistically significant.

Analysis of variance suggested a significant positive correlation between arterial pressure and plasma noradrenaline concentration (table I). There was no significant correlation between arterial pressure and adrenaline or dopamine concentrations.

TABLE I. *Changes in mean arterial pressure and arterial catecholamine concentration. Time intervals relative to the time of intubation. Pre-A = before onset of anaesthesia. Pre-I = after onset of anaesthesia but before intubation. Mean arterial pressure was taken as diastolic + one-third pulse pressure and expressed in mm Hg (± SEM). The arterial plasma catecholamine concentrations are expressed in pmol ml^{-1} (± SEM).* *P < 0.05; **P < 0.01 *(comparisons were made with the values immediately preceding these in the table)*

Time	Pre-A	Pre-I	1 min	5 min	10 min	*r*
Mean arterial pressure	100±5.2	77±6.6*	122±5.9**	90±6.5	83±6.1	0.40 (*P*<0.001)
Noradrenaline	1.82±0.24	1.43±0.24	2.43±0.27*	1.71±0.40	1.77±0.34	
Adrenaline	0.61±0.19	0.21±0.02	0.36±0.06	0.22±0.05	0.44±0.15	
Dopamine	0.67±0.20	0.76±0.15	0.75±0.11	0.59±0.09	0.75±0.14	
n	16	8	16	16	16	

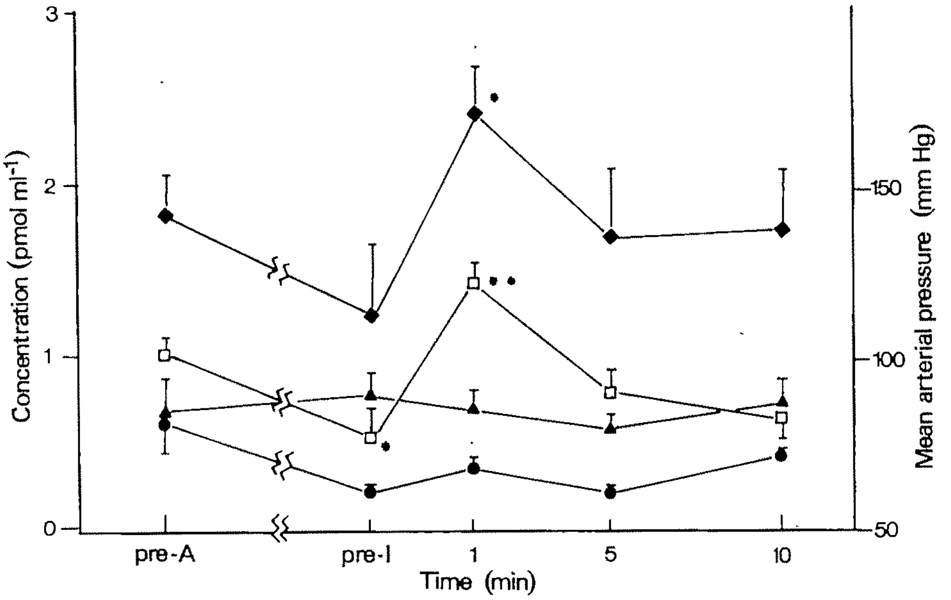

FIG. 1. Changes in mean arterial pressure (□) and arterial noradrenaline (◆), adrenaline (●) and dopamine (▲) concentrations associated with endotracheal intubation. *$P < 0.05$; **$P < 0.01$. Pre-A = before anaesthesia; pre-I = after onset of anaesthesia, but before intubation. Significant and correlated increases in arterial pressure and plasma noradrenaline concentrations were noted 1 min after intubation.

DISCUSSION

The pre-intubation plasma catecholamine concentrations found in this study are similar to those reported by Bühler and others (1978) and Saar and Gordon (1979). The important difference, however, is that blood samples from our patients were arterial and not venous. Central venous blood samples would have resulted in increased plasma noradrenaline concentrations since noradrenaline is taken up by the lungs to a greater extent than other catecholamines (Fishman and Pietra, 1974).

The most significant findings were increases in arterial pressure and plasma noradrenaline concentration following intubation. The magnitude of the increases in pressure was considerable (115 mm Hg systolic and 54 mm Hg diastolic in one subject) and paralleled the increases in plasma noradrenaline concentration. The plasma adrenaline and dopamine concentrations did not change significantly. These results suggest that intubation is associated with a significant increase in sympathetic nerve activity.

Our findings are relevant to the management of patients at risk from increases in arterial pressure, for example, patients with intracranial aneurysms. Prophylactic measures to block the enhanced sympathetic activity following intubation may be required and the use of purely beta-blocking agents would seem to be an incomplete solution.

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VARIATIONS DANS LES CONCENTRATIONS DE CATECHOLAMINE DANS LE PLASMA PENDANT UNE INTUBATION ENDOTRACHEALE

RESUME

On a surveillé sur 16 patients subissant une intubation endotrachéale, les variations se produisant dans la pression artérielle et dans les concentrations artérielles de noradrénaline, d'adrénaline et de dopamine. On a constaté des augmentations significatives de la pression artérielle moyenne et de noradrénaline dans le plasma. Les augmentations de pression artérielle ont été reliées à l'augmentation des concentrations de noradrénaline. Les concentrations d'adrénaline et de dopamine n'ont pas sensiblement changé après l'intubation. Les résultats obtenus laissent penser à une réaction à prédominance sympathique pendant l'intubation et le besoin de prophylaxie chez les malades exposés au danger.

KONZENTRATIONSÄNDERUNGEN VON CATECHOLAMIN IM PLASMA BEI ENDOTRACHEALROHREINFÜHRUNG

ZUSAMMENFASSUNG

Die Veränderungen bei arteriellem Druck und arteriellen Konzentrationen von Noradrenalin, Adrenalin und Dopamin wurden bei 16 Patienten während Endotrachealrohreinführung untersucht. Wesentliche Anstiege des mittleren arteriellen Druckes und von Plasma-Noradrenalin wurden festgestellt. Der arterielle Druckanstieg hing mit dem Noradrenalin-Anstieg zusammen. Adrenalin- und Dopaminkonzentrationen änderten sich nach der Rohreinführung nicht wesentlich. Die Resultate zeigen eine vorwiegend sympathische Reaktion während der Einführung, und die Notwendigkeit für Prophylaxe bei gefährdeten Patienten.

CAMBIOS EN LAS CONCENTRACIONES DE CATECOLAMINA DEL PLASMA DURANTE LA INTUBACION ENDOTRAQUEAL

SUMARIO

Se vigilaron los cambios de la presión y de la concentración arterial ocasionados por la noradrenalina, la adrenalina y la dopamina en 16 pacientes sometidos a intubación endotraqueal. Se apreciaron cambios significativos en la presión arterial media y en la noradrenalina del plasma. Los cambios en la presión arterial se asociaron con los incrementos en las concentraciones de noradrenalina. Las concentraciones de adrenalina y de dopamina no cambiaron significativamente durante la intubación. Los resultados obtenidos sugieren una respuesta predominantemente simpática durante la intubación y la necesidad de profilaxis en aquellos pacientes en condiciones de riesgo.

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LOW I.V. REGIONAL ANALGESIA WITH BUPIVACAINE FOR HAND SURGERY

M. ROUSSO, H. DREXLER, E. VATASHSKY, H. ASHUR AND H. B. ARONSON

SUMMARY

A forearm tourniquet for i.v. regional analgesia of the hand, using doses of bupivacaine smaller than in the conventional (upper arm) method, produced successful analgesia in 98 of 102 patients. In 63 patients bupivacaine 50 mg or less was adequate, while in 33 the dosage was between 60 and 75 mg. No toxic effect was noted. This technique permits surgery of the hand, wrist and distal forearm.

The i.v. injection of an analgesic agent into an exsanguinated upper limb using a double-cuffed tourniquet placed above the elbow is a well-recognized and relatively safe technique for producing analgesia of the hand and tourniquet site (Holmes, 1963; Merle d'Aubigné, Tubiana and Vincent, 1965). Bupivacaine (Ware, 1975), although relatively more toxic than lignocaine (Scott, 1975), is preferred because much of it remains bound to nerve tissue even after release of the tourniquet (Rousso et al., 1978a). The persisting analgesia enables surgery to be continued with, or if necessary without, re-establishing ischaemia. However, because 30–40 ml (75–200 mg) of 0.25–0.5% bupivacaine is needed (Rousso et al., 1978a) to fill the veins of the arm, systemic toxic effects may develop if the tourniquet is released too soon or too rapidly. Convulsions (Moore et al., 1977), loss of consciousness and cardiovascular depression may occur and cardiac arrest has been reported (Albright, 1979). Lately we presented evidence that when the tourniquet was applied to the forearm below the level of the elbow, satisfactory ischaemia of the hand and wrist could be obtained in 99% of patients (Rousso et al., 1978a,b), permitting surgery of the wrist and distal forearm, despite previous reports to the contrary (Bunnell, 1964). The purpose of this study was to determine if the i.v. regional injection of significantly less bupivacaine into the very much smaller area of exsanguinated forearm could produce analgesia of the hand as good as that produced by the conventional method of i.v. regional anaesthesia.

PATIENTS AND METHODS

One hundred and two patients (48 male, 54 female, aged 15–76 yr) undergoing various operations of the hand and wrist, including soft tissues, nerves, tendons (78 patients) bone and joints (24 patients), were investigated. One hour before surgery the patients were premedicated i.m. with pethidine 1 mg kg^{-1}, droperidol 2.5 mg and atropine 0.5 mg. Day care patients were premedicated with oral diazepam 5–10 mg only. An infusion of 5% dextrose was commenced on the contralateral arm and a plastic cannula inserted to a distal vein on the affected hand, perferably on its dorsum. All patients received oxygen by mask, and indirect arterial pressure and e.c.g. were monitored. In the operating theatre a double-cuff tourniquet was applied to the upper third of the affected forearm, and exsanguination of the hand and lower forearm was performed. A pressure of 300 mm Hg was applied to the proximal tourniquet and, if there was any evidence of early capillary refill this technique was abandoned and the patient excluded from the study (two patients). If there was no capillary refill, after 2–3 min, 0.5% bupivacaine 10 ml (50 mg, without preservative) was injected through the cannula of the affected hand. Analgesia of the wrist and palm commenced within 2 min and was usually complete after a further 5 min. If not, an extra 5–10 ml of 0.5% bupivacaine was injected through the cannula with the intention of increasing both the dose of analgesic agent and the injected volume. In 34 patients, we

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added 5–10 ml of normal saline instead of bupivacaine, surmising that the increased volume would increase the venous pressure and force open the valves of the hand, to permit distal flow of the analgesic drug. The maximum volume injected was 20 ml in all except two patients. Successful analgesia was usually preceded by distension of the veins on the dorsum of the hand. The venous cannula was removed and surgery commenced. If tourniquet pain occurred during operation, the distal tourniquet was substituted for the proximal one. At the conclusion of surgery, the tourniquet was released slowly and cardiorespiratory monitoring performed for a further 30 min at least.

In 14 patients, more than one operation was performed on the same hand during one session (in patients with carpal tunnel syndrome, surgery was also performed for trigger finger (two patients), epineural neurolysis of the median nerve (two patients) and synovectomy of the flexor tendons (three patients)).

Analgesia of the operative area and tourniquet site was evaluated according to the following criteria: *excellent* = complete analgesia requiring no further medication during the course of surgery other than diazepam 5–10 mg i.v.; *satisfactory* = analgesia acceptable but classified as good only after the addition of either pethidine 25–50 mg i.v. or a small amount of local anaesthetic; *poor* = no analgesia, necessitating a change in anaesthetic technique.

RESULTS

Regional analgesia of the lower forearm and hand was obtained successfully in 98 (96%) of the 102 patients who received low i.v. regional block with bupivacaine. Analgesia was excellent in 76 patients and satisfactory in 22. Bupivacaine 60 mg or less gave adequate analgesia in all except one of 85 patients (table I).

The volume of bupivacaine injected was 10 ml in 25 patients, 12–15 ml in 47 patients, and 16–20 ml in 26 patients. The four failures had 50, 75, 90 and 100 mg contained in volumes of 10, 15, 25 and 30 ml respectively.

Results were classified according to the following operative sites: wrist, palm, metacarpo-phalangeal area and digits (table II). Analgesia was satisfactory in all 38 patients undergoing operations of the wrist and palm. However, there were four failures amongst the 64 patients who underwent surgery at or distal to the metacarpo-phalangeal area.

The duration of surgery ranged from 15 to 95 min (average 39 min) and the duration of ischaemia was 22–100 min (average 44 min).

Tourniquet pain necessitating change of cuff occurred in 74 operations, mainly in those lasting more than 30 min. One tourniquet was released 22 min before the end of surgery for reconstruction of the ulnar nerve at wrist level lasting 82 min.

No toxic effects were noted in any patient and arterial pressure, heart rate and e.c.g. were stable during the investigation. Mild venous congestion was infrequent and did not disturb surgery.

DISCUSSION

The results of this preliminary investigation indicate that low i.v. regional anaesthesia using a forearm tourniquet produces excellent analgesia of the hand and wrist in the majority of patients. The amount of bupivacaine usually required for this technique (50–75 mg) is small, compared not only with the 150–200 mg generally used (Rousso et al., 1978a), but also with the reduced amount (1.5 mg kg^{-1}) recommended by Ware (1975) for the conventional technique using an upper arm tourniquet. Therefore, low i.v. regional anaesthesia greatly decreases the tendency for systemic side effects.

TABLE I. *Results of low i.v. regional anaesthesia as related to dose of bupivacaine*

		Analgesia			Successful analgesia	
Dose	No. of patients	Excellent	Satisfactory	Poor	No.	%
37.5 mg	2	2	—	—	2	100
50 mg	62	49	12	1	61	98
60 mg	21	17	4	—	21	100
75 mg	13	6	6	1	12	92
80–100 mg	4	2	—	2	2	50
Total	102	76	22	4	98	96

TABLE II. *Results of low i.v. regional anaesthesia as related to the site of operation (102 patients)*

Site of operation	No. of patients	Analgesia			Successful analgesia	
		Excellent	Satisfactory	Poor	No.	%
Wrist	26	22	4	—	26	100
Palm	12	8	4	—	12	100
Metacarpo–phalangeal area	26	17	7	2	24	92
Digits	38	29	7	2	36	92
Total	102	76	22	4	98	96

In two independent studies (Widman, 1975; Moore et al., 1978) the inadvertent intravascular injection of bupivacaine during other forms of regional analgesia was not followed by c.n.s. or cardiovascular ill-effects when the dose of bupivacaine was less than 50 mg. This was equal to the total dose of bupivacaine needed to produce successful analgesia in 60% of our patients, so that the safety of i.v. regional analgesia should be greatly enhanced by this technique. Particularly good results were obtained in the region of the wrist where analgesia was excellent in 84%, and satisfactory in 16% of the patients, with no failures. Results were acceptable in the palm, where analgesia was excellent in 67% and satisfactory in the remaining 33% of patients. The results were less successful in surgery of the metacarpo–phalangeal and digital areas, where four of 64 cases were failures. These four were in operations below the distal palmar crease and might be explained by an insufficient volume of analgesic solution. It has been stated that, for good analgesia of the finger-tips, a volume of 50–60 ml of analgesic solution is required when using upper-arm i.v. regional anaesthesia (Atkinson, Bushman and Lee, 1977). Individual lack of sensitivity to the drug may be a factor.

We do not have enough data to draw final conclusions as regards a correlation between the dose and volume of analgesic used. It is our clinical impression, however, that dose is the critical factor.

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ANALGESIE REGIONALE I.V. INFERIEURE PAR BUPIVACAINE DANS LA CHIRURGIE DE LA MAIN

RESUME

Chez 98 patients sur 102 traités, on a obtenu une analgésie réussie au moyen d'un garrot sur l'avant-bras et de doses de bupivacaine inférieures à celles utilisées dans la méthode traditionnelle (partie supérieure du bras), pour obtenir une analgésie régionale i.v. de la main. Pour 63 patients, 50 mg ou moins de bupivacaine suffirent tandis que pour 33 autres, la dose oscillait entre 60 et 75 mg. Aucun effet toxique n'a été observé. Cette technique permet d'effectuer des opérations chirurgicales de la main, du poignet et de la région distale de l'avant-bras.

LEICHTE INTRAVENÖSE LOKALANALGESIE MIT BUPIVACAIN FÜR HANDOPERATIONEN

ZUSAMMENFASSUNG

Eine Unterarm-Abschnürbinde für intravenöse Lokalanalgesie der Hand mit Bupivacain-Dosen, die kleiner waren als bei der koventionellen Oberarmmethode bewirkte erfolgreiche Analgesie bei 98 von 102 Patienten. Bei 63 Patienten waren 50 mg oder weniger ausreichend, während die Dosis bei 33 Patienten zwischen 60 und 75 mg Bupivacain lag. Toxische Effekte gab es nicht. Diese Methode gestattet Eingriffe in der Hand, dem Gelenk und dem distalen Unterarm.

ANALGESIA REGIONAL I.V. INFERIOR CON BUPIVACAINA PARA CIRUJIA DE LA MANO

SUMARIO

Mediante un torniquete del antebrazo y dosis de bupivacaina menores de la usada en el método convencional (parte superior del brazo) aplicados con miras a obtener la analgesia regional i.v. de la mano, se obtuvo una analgesia exitosa en 98 de los 102 pacientes tratados. Bastaron unos 50 mg o menos de bupivacaina para 63 de los pacientes, mientras que para 33 otros, se usó una dosis de 60 a 75 mg. No se observó efecto tóxico alguno. Esta técnica permite efectuar la cirujía de la mano, de la muñeca y de la región distal del antebrazo.

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CORACOID BLOCK—A SAFE AND EASY TECHNIQUE

K. WHIFFLER

SUMMARY

A method of blocking the brachial plexus using an infraclavicular approach is described. Compared with the supraclavicular approach, pulmonary complications do not occur and compared with the axillary approach a higher level of analgesia can be obtained and a potentially septic area is not traversed. However, the level of anaesthesia is at a lower level than that obtained from the supraclavicular approach.

The high frequency of pneumothorax and phrenic nerve paralysis which accompanies the standard supraclavicular approach to the brachial plexus is disadvantageous (Lee, 1968; Bonica, 1969; Wylie and Churchill Davidson, 1972), although in the healthy patient these complications may not be serious problems. However, since brachial plexus block is frequently indicated in poor-risk subjects any form of respiratory embarrassment may produce serious consequences. Therefore, any technique which permits blockade of the brachial plexus without the risk of pulmonary complications would be advantageous.

METHOD

At the level of the coracoid process the three divisions of the brachial plexus form the lateral, posterior and medial cords. These three structures, and the axillary artery and vein, are encased in the axillary sheath and the intercosto–brachial nerve runs in close proximity to this sheath (Johnston and Whillis, 1954; Boileau Grant, 1956). This would appear to be a logical site at which to block the brachial plexus.

At this level the skin, pectoralis major and pectoralis minor muscles collectively form a thick tissue layer. In Boileau Grant's *Atlas of Anatomy* the axillary sheath and its contents appear to be far from the coracoid process. However, if the shoulder is depressed and the arm abducted, the axillary sheath and contents could be brought closer to the coracoid process.

Preliminary studies

A feasibility study was undertaken on anatomical specimens in the dissection room, and it became apparent that the brachial plexus could be safely approached from the anterior aspect of the axilla.

In order to determine if the plexus could be blocked high in the axilla, without appreciable risk of pulmonary complications, the proposed coracoid block was performed on fresh cadavers. A solution of methylene blue was used and its site of deposition and route of injection were subsequently dissected to determine the accuracy of placement of the solution. It was found that a large area of the axilla was stained by the dye, and that the cords of the brachial plexus could be bathed readily with methylene blue solution.

The next step was to assess the risk of penetrating the thoracic cavity and, using this approach, deliberate attempts were made to penetrate the cavity, but it proved impossible to penetrate. In addition, the phrenic nerve could not be blocked accidentally. Following this evaluation in cadavers a trial was undertaken on volunteers who gave informed consent.

Patients

This technique was used on 40 patients all of whom were adult muscular males involved in a labouring capacity in heavy industry. Informed consent was obtained from each patient.

Technique

The patient lay supine with the head turned to the side opposite to that on which the block was to be performed. The relevant shoulder was depressed and the arm abducted approximately 45° from the chest wall (fig. 1). The midpoint of the clavicle was identified and the subclavian artery

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palpated. The artery was followed laterally until it disappeared under the clavicle and this point was marked with a skin pen (X1, fig. 2).

The coracoid process was identified and marked with a skin pen. The axillary artery was palpated with the index finger as high as possible in the axilla. The thumb was placed on the anterior surface of the chest wall over the site at which the index finger palpated the axillary artery. This point was marked with a skin pen (X2, fig. 2). In most instances this point will be found to lie in the delto–pectoral groove, just below the head of the humerus. The depth at which the axillary sheath and contents lie could then be gauged by estimating the distance between the thumb and the index finger and gave an indication of the depth to which the needle had to be inserted. Points X1 and X2 were joined by a line with the skin pen. It was noted that in most cases this line passed immediately inferior and medial to the coracoid process.

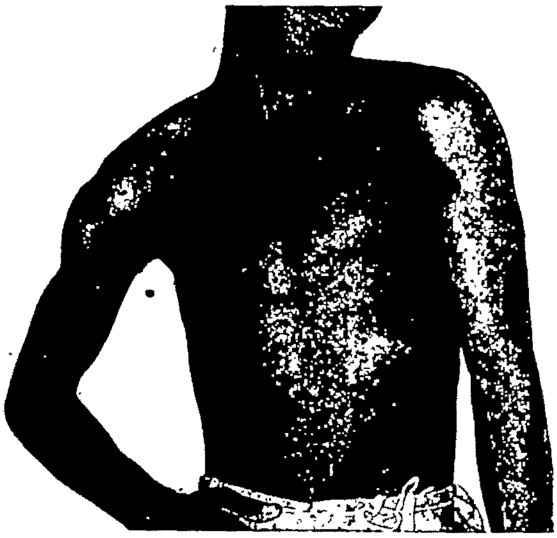

FIG. 1. Position of patient for coracoid block.

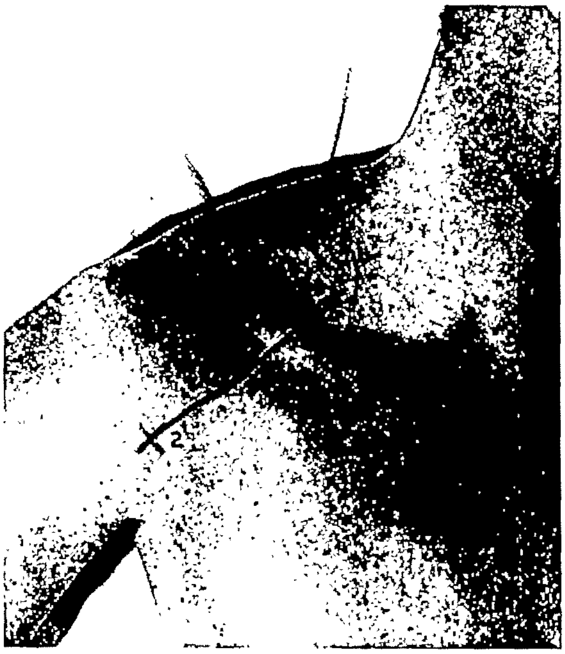

FIG. 2. Markings and surface anatomy for the coracoid block.

The skin over the coracoid process was cleaned and, using a 21-gauge 51-mm needle attached to a 20-ml syringe, the skin was punctured inferiomedial to the coracoid process and the line joining X1 and X2 transected at the depth which had previously been estimated by the distance between the thumb and index finger. The needle was usually at right angles to the skin. Because of the depth at which the axillary sheath and contents lie it was often necessary to insert the needle almost up to its hub.

After aspiration, approximately 12 ml of local anaesthetic agent was injected. The needle was withdrawn 1 cm and the procedure of aspiration and injection repeated. This manoeuvre was repeated twice in a muscular person (36 ml total volume) and once in an ectomorphic patient (24 ml). This distributed the local anaesthetic solution around the neurovascular bundle. When doubt existed about striking the axillary sheath and contents with the first injection, the needle was withdrawn until the bevel lay just beneath the surface of the skin, and it was then advanced in a slightly angled direction either inferiorly to the first injection, or superiorly to the first injection, depending upon where the plexus was thought to lie. The procedure of withdrawal, aspiration and injection was carried out as described previously. Care was taken not to exceed the total calculated safe dose of local anaesthetic drug.

The area infiltrated by this procedure can be clearly seen in the x-ray photograph which was obtained by adding Conray 250 to the local anaesthetic agent. It will be seen that the local anaesthetic has spread to involve the whole axilla (fig. 3). There is a layer of muscle between the chest wall and axilla but in no patient in whom this technique

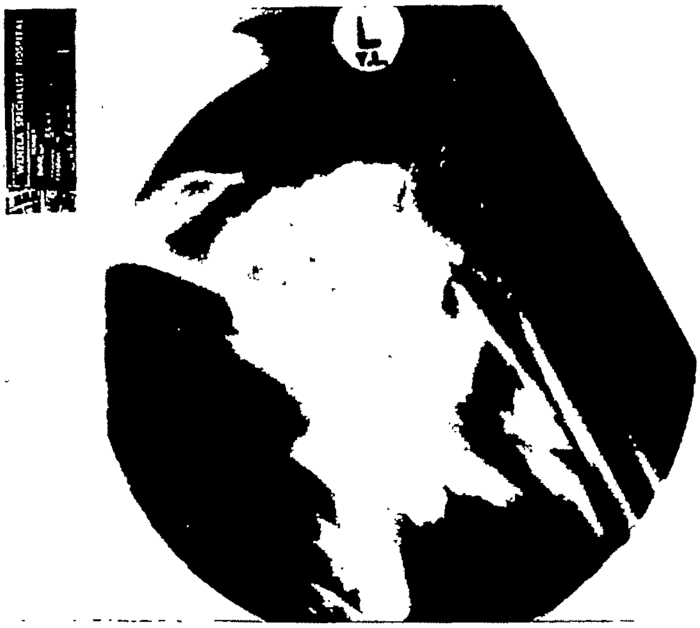

FIG. 3. X-ray showing area infiltrated by means of the procedure.

has been used was this muscle infiltrated. The cords of the brachial plexus can be seen in the axilla, illustrating that the whole of the axilla and its contents have been bathed in the local anaesthetic agents.

Drugs and equipment

Premedication consisted of flunitrazepam 1 mg i.m. 1 h before operation. Equal volumes of 2% lignocaine and 0.5% bupivacaine in 1 : 2 000 000 ephedrine were used. Doses did not at any time exceed lignocaine 7 mg kg^{-1} or bupivacaine 2 mg kg^{-1}. A maximum dose calculated on a weight basis was drawn up for each patient.

Three 20-ml syringes and one 51-mm, 21-gauge medium bevel needle were required. (The usual 38-mm, 21-gauge needle is not sufficiently long for the procedure described.)

The usual volumes used were 0.5% bupivacaine 30 ml (150 mg) and 2% lignocaine 30 ml (600 mg). Out of this total volume of 60 ml only 40 ml was usually used.

RESULTS

The axillary artery was punctured in 50% of patients, but there was no discernible evidence of spasm or haematoma formation. Sensory block occurred readily, but motor blockade was not easily obtained unless 2% lignocaine was used.

The technique failed in three patients and this was ascribed to a faulty identification of landmarks and faulty technique.

Sensory block occurred in every successful case from C5–6 to T2. (The whole of the axilla was anaesthetized and it was not necessary to block the intercostobrachial nerve.) The use of a tourniquet applied to the upper arm in order to produce a bloodless field caused no discomfort to the patients.

The onset of analgesia was slightly longer than experienced using the normal supraclavicular approach, the average time being 10–20 min.

DISCUSSION

Montgomery and colleagues (1973) described a technique in which the brachial plexus was blocked using an infraclavicular approach. Their method required many more landmarks and that the arm be abducted to 90°. Using their technique the depth at which the plexus lies is not determined and use must be made of a nerve stimulus to identify the plexus. A different technique is described here in which the brachial plexus can be blocked at a high level in the axilla using the "coracoid" approach. This is a simpler approach and does not require stimulation of the nerve. An advantage of the coracoid approach is that pulmonary complications do not occur.

The block obtained was at a level sufficiently high to apply a constrictive tourniquet without discomfort to the upper arm and in no patient was it necessary to block the intercostobrachial nerve as a separate procedure (Lee, 1968; Wylie and Churchill Davidson, 1972).

The injection appeared to be less distressing to the patient than the supraclavicular approach. In addition, the method has an advantage over the axillary approach to the plexus in that the introduction of local anaesthetic solution through a potentially septic area is avoided.

The coracoid approach offers all the advantages of the supraclavicular approach without any of the major disadvantages. However, the level of the block is lower than that obtained from a supraclavicular block, but the level of anaesthesia is higher than that obtained from an axillary block (Bonica, 1969; Wylie and Churchill Davidson, 1972).

Careful identification of landmarks and strict attention to the technique described is important to avoid failure. A slightly higher concentration of local anaesthetic agent appears to be necessary than that needed for supraclavicular block, presumably because of the thickness of the axillary sheath, and the block is slightly longer in onset; the thick axillary sheath is probably responsible.

Adequate sensory block occurs readily, but motor blockade is not complete unless a stronger concentration of anaesthetic agent is used.

Infraclavicular block of the brachial plexus would appear to be the method of choice for surgery to the forearm and hand. Also, bilateral blocks may be carried out without fear of producing bilateral phrenic nerve paralysis.

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BLOCAGE CORACOIDE—TECHNIQUE SUR ET FACILE

RESUME

Une méthode de blocage du plexus brachial par une voie infraclaviculaire est décrite dans cet article. Par comparaison à la voie supraclaviculaire il ne se produit aucune complication pulmonaire, et par rapport à la voie axillaire, on obtient une meilleure analgésie. Ceci évite de traverser une zone susceptible de devenir septique. Quoiqu'il en soit, le niveau d'anesthésie est inférieur à celui que l'on obtient par la voie supraclaviculaire.

SICHERE UND EINFACHE METHODE DER BRACHIALPLEXUS-BLOCKIERUNG

ZUSAMMENFASSUNG

Eine Methode zur Blockierung des Brachialplexus' auf infraclavikulärem Wege wird beschrieben, Verglichen mit der supraclavikulären Methode treten dabei keine Lungenkomplikationen auf, und verglichen mit der axillaren Methode wird stärkere Analgesie erzielt und keine potentiell septische Stelle überquert. Allerdings ist die so erzielte Narkosetiefe geringer als die, die mit der supraclavikulären Methode erzielt wird.

BLOQUEO CORACOIDEO—UNA TECNICA SEGURA Y FACIL

SUMARIO

Se describe un método de bloqueo del plexus braquial usando un método infraclavicular. En comparación con el método supraclavicular, no tienen lugar complicaciones pulmonares y en comparación con el método axilar puede obtenerse un mayor nivel de analgesia, no pasando así por una zona potencialmente séptica. Sin embargo, el nivel de anestesia es de un nivel inferior al obtenido mediante el método supraclavicular.

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EFFECT OF NEOSTIGMINE AND PYRIDOSTIGMINE ON THE PLASMA CHOLINESTERASE ACTIVITY

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SUMMARY

The effect of neostigmine 0.05 mg kg^{-1} or pyridostigmine 0.25 mg kg^{-1} on serum cholinesterase activity was investigated in 20 adult patients undergoing elective surgery. Both drugs produced marked depression of enzymatic activity. The maximal depression was observed in samples taken 5 min after injection. The maximal percentage depression of enzymatic activity was not significantly different in the two drug groups. However, at 30–60 min after injection, the degree of depression was less in the neostigmine group. This may be attributed to the different plasma clearances of neostigmine and pyridostigmine.

Stoelting (1976) demonstrated that the inhibition of plasma cholinesterase by pyridostigmine was more pronounced and prolonged than the inhibition produced by neostigmine. In contrast, Sunew and Hicks (1978) did not find any significant difference between the inhibitory properties of the two drugs. This study was designed to reinvestigate the effects of neostigmine and pyridostigmine on the plasma cholinesterase activity.

PATIENTS AND METHODS

Twenty adult patients undergoing elective surgical procedures were studied. They were 15 male and five female patients, aged between 18 and 50 yr and weighing 60–80 kg. No patient had evidence of renal, hepatic, or other systemic disease. Premedication was with atropine 0.6 mg, pethidine 75 mg and phenergan 25 mg i.m. 1 h before surgery. Anaesthesia was induced with thiopentone 5 mg kg^{-1}. Suxamethonium 1.5 mg kg^{-1} was administered i.v. and the trachea intubated. Anaesthesia was maintained with nitrous oxide in oxygen (2:1); alcuronium was administered to maintain neuromuscular blockade. At the end of surgery, neuromuscular blockade was antagonized in 10 patients with a mixture of neostigmine 0.05 mg kg^{-1} and atropine 0.02 mg kg^{-1} i.v. The other 10 patients received pyridostigmine 0.25 mg kg^{-1} and atropine 0.02 mg kg^{-1}.

Plasma cholinesterase activity

Venous samples for the estimation of serum cholinesterase activity were taken from the arm opposite to that used to administer the anticholinesterase drug. A control sample was taken from all patients 5 min before the injection of neostigmine or pyridostigmine. Sampling was continued at 5 min, 15 min, and every 15 min for 120 min after injection. Serum cholinesterase activity was assayed according to the method described by Kalow and Genest (1957) (normal values in our laboratory—220 ± 70 i.u. litre^{-1}). The percentage depression of enzyme activity was compared in the two groups. Student's t test was used to analyse the data; $P < 0.05$ was considered as statistically significant.

RESULTS

The baseline serum cholinesterase activity before injection of neostigmine or pyridostigmine was within the normal range. In the neostigmine group, mean serum cholinesterase activity was 264.6 iu litre^{-1} (SEM 21.7) and the dibucaine number ranged from 73 to 90. In the pyridostigmine group, the dibucaine number ranged from 75 to 86, and the mean serum cholinesterase activity was 232.2 iu litre^{-1} (SEM 19.2). There were no significant differences between the two groups.

The effects of neostigmine 0.05 mg kg^{-1} and pyridostigmine 0.25 mg kg^{-1} on the serum cholinesterase activity at the different time intervals following injection are presented in figure 1. Following neostigmine, the serum cholinesterase

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activity was significantly less than baseline at 5 and 15 min. In the pyridostigmine group, the enzyme activity was significantly less than control throughout the period of observation, which lasted for 120 min.

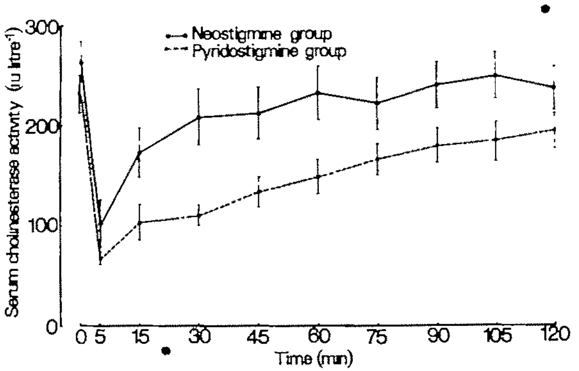

FIG. 1. The effect of neostigmine 0.05 mg kg^{-1} and pyridostigmine 0.25 mg kg^{-1} on the serum cholinesterase activity (mean ± SEM), at various times following injection.

The percentage depression of serum cholinesterase activity following both drugs was maximal in the initial samples taken 5 min after injection; the mean maximal percentage depression following pyridostigmine was 70.37% (SEM 2.36), while that following neostigmine was 63.44% (SEM 7.03) (fig. 2); there was no significant difference between the two means. However, at 30, 45, and 60 min, the percentage depression was significantly less in the neostigmine group than in the pyridostigmine group.

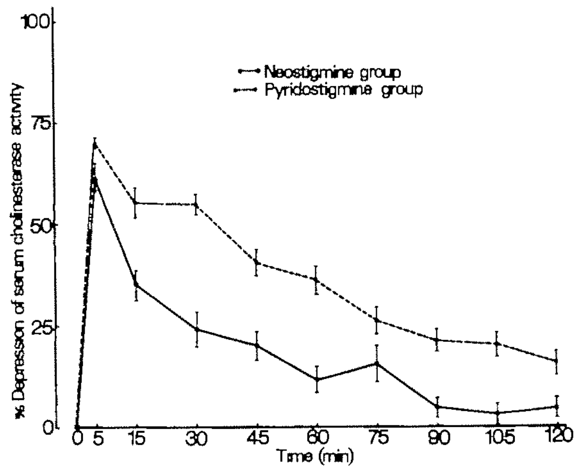

FIG. 2. Mean (± SEM) percentage depression of the serum cholinesterase activity following neostigmine 0.05 mg kg^{-1} or pyridostigmine 0.25 mg kg^{-1}.

DISCUSSION

The present report shows that neostigmine and pyridostigmine, in clinical doses used for the antagonism of neuromuscular block, can rapidly depress plasma cholinesterase activity. The maximum depression of activity was observed in the samples taken 5 min after the injection i.v. of either drug. The maximal percentage depression of enzyme activity was not significantly different in the two groups. However, at 30–60 min, the degree of depression was significantly less in the neostigmine group. This suggests that neostigmine produces a shorter duration of depression of the serum cholinesterase activity than that produced by an equipotent dose of pyridostigmine. Such a difference may be attributed to the different plasma clearance of neostigmine and pyridostigmine. Neostigmine has a shorter half-life than pyridostigmine, and is readily eliminated from the plasma (Baker et al., 1978; Williams, Calvey and Chan, 1978).

Our results confirm Stoelting's observations (1976), that pyridostigmine produces a longer duration of enzyme depression than neostigmine, but are different from the findings of Sunew and Hicks (1978) who showed that equipotent doses of neostigmine and pyridostigmine produce similar depression of the plasma cholinesterase activity. This discrepancy may be attributed to the relatively high doses used by these authors.

Serum cholinesterase is responsible for the metabolic breakdown of suxamethonium and other drugs used in anaesthesia, such as the ester type of local anaesthetics. In patients with normal serum cholinesterase activity, the enzyme determines the rate of hydrolysis of suxamethonium and hence the duration of its neuromuscular blockade (Kalow, 1959). Neostigmine, which inhibits serum cholinesterase has been shown to potentiate the neuromuscular block of suxamethonium (Baraka, 1977; Sunew and Hicks, 1978). Potentiation of suxamethonium blockade has been observed also following pyridostigmine–suxamethonium interaction (Bentz and Stoelting, 1976; Sunew and Hicks, 1978). One should always consider the likelihood of a decrease in serum cholinesterase activity whenever anaesthesia is administered to patients who have recently received neostigmine or pyridostigmine for antagonism of competitive neuromuscular blockade (Stoelting, 1976), or to myasthenic patients who receive anticholinesterase therapy on a regular basis (Foldes and Smith, 1966).

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EFFET DE LA NEOSTIGMINE ET DE LA PYRIDOSTIGMINE SUR L'ACTIVITE DE LA CHOLINESTERASE DANS LE PLASMA

RESUME

On a fait des recherches sur les effets qu'a la néostigmine 0,05 mg kg^{-1} ou la pyridostigmine 0,25 mg kg^{-1} sur l'activité de la cholinestérase dans le plasma, sur 20 patients adultes devant subir une intervention chirurgicale à froid. Ces deux préparations ont produit une dépression marquée de l'activité enzymatique. La dépression maximale a été observée dans les échantillons prélevés 5 min après l'injection. Le pourcentage maximal de dépression de l'activité enzymatique n'a pas été très différent dans les deux groupes de médicaments. Toutefois, entre 30 et 6 min après l'injection, le degré de dépression a été moindre dans le groupe traité à la néostigmine. Ceci peut être attribué aux différents coefficients d'épuration de la néostigmine et de la pyridostigmine contenues dans le plasma.

WIRKUNG VON NEOSTIGMIN UND PYRIDOSTIGMIN AUF DIE PLASMA-CHOLINESTERASE-AKTIVITÄT

ZUSAMMENFASSUNG

Die Wirkung von Neostigmin 0,05 mg kg^{-1} oder von Pyridostigmin 0,25 mg kg^{-1} auf Serum-Cholinesterase-Aktivität wurde bei 20 erwachsenen Patienten bei verschiedenen Operationen verglichen. Beide Drogen führten zu einer signifikanten Unterdrückung der Enzym-Aktivität, maximal bei Proben, die 5 Minuten nach der Injektion entnommen wurden. Der diesbezügliche Unterschied zwischen den beiden Drogengruppen war nicht signifikant, was den maximalen Prozentsatz der Unterdrückung betraf. Aber 30–60 Minuten nach der Injektion war die Unterdrückung in der Neostigmin-Gruppe geringer. Dies könnte auf die verschiedenartige Plasmaausscheidung von Neostigmin und von Pyridostigmin zurückzuführen sein.

EFECTOS DE LA NEOSTIGMINA Y DE LA PIRIDOSTIGMINA EN LA ACTIVIDAD DE LOS COLESTERASES DEL PLASMA

SUMMARIO

Se investigaron los efectos de 0,05 mg kg^{-1} de neostigmina o de 0,25 mg kg^{-1} de piridostigmina sobre la actividad del suero de colinesterases en 20 pacientes adultos sometidos a operación quirúrjica electiva. Ambas drogas produjeron una notable depresión de la actividad enzimática. La máxima depresión se observó en muestras tomadas 5 minutos después de la inyección. El porcentaje máximo de depresión de la actividad enzimática no fue significativamente diferente en los dos grupos de drogas. No obstante a los 30–60 minutos después de la inyección el grado de depresión fue menor en el grupo de neostigmina. Esto se atribuyó a la diferente eliminación de neostigmina y de piridostigmina en el plasma.

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RELATIONSHIP BETWEEN DECAY OF PLASMA CONCENTRATION OF FAZADINIUM AND RECOVERY FROM ITS NEUROMUSCULAR BLOCKING EFFECT

A. A. D'HOLLANDER, P. DUVALDESTIN, D. HENZEL, C. DELCROIX AND J. M. DESMONTS

SUMMARY

The relationship of the time-course of the decay of plasma concentration of fazadinium and neuromuscular block has been investigated after i.v. administration of 0.75 mg kg^{-1} to six anaesthetized patients. The pharmacokinetics of fazadinium were analysed according to a two-compartment open model. A significant correlation was found between the plasma concentration of fazadinium and the twitch height (TH) values during recovery from the block ($P < 0.001$). The mean total plasma concentrations for 25, 50 and 75% TH recovery were: 1.90 ± 0.17; 1.44 ± 0.18 and 1.08 ± 0.12 µg ml^{-1}, respectively. Elapsed time between fazadinium administration and the TH recovery to 50% (0–TH_{50}) and the recovery period TH_{25-75} were 47 ± 4 min and 25 ± 2 min, respectively. Plasma log decay rate of fazadinium during TH_{25-75} period ($K_{app\ 25-75}$) was: 0.0249 ± 0.0032 min^{-1}. Significant correlations ($P < 0.01$) were observed between the elimination rate constant (k_{10}) of the pharmacokinetic model, $K_{app\,25-75}$ ($P < 0.01$) and the pharmacodynamic parameters: time interval 0–TH_{50} and recovery rate TH_{25-75}. These results showed that part of the individual pharmacodynamic variation had its origin in the interindividual pharmacokinetic variation.

Fazadinium bromide (Bolger et al., 1972; Arora et al., 1973; Waud, 1977) has pharmacokinetic properties which are now established in normal man (Duvaldestin et al., 1978) and in patients with renal (Duvaldestin et al., 1979) and hepatic failure (Duvaldestin et al., 1980). A pharmacodynamic study combining simultaneous measurement of the plasma concentration and the degree of paralysis, by twitch-height recording, has never been undertaken for this agent alghough this has been extensively studied for tubocurarine (Matteo, Spector and Horowitz, 1974; Sheiner et al., 1979) and pancuronium (Agoston et al., 1977; Hull et al., 1978; Shanks, Somogyi and Triggs, 1979).

We describe the simultaneous evolution of the plasma concentration and of paralysis and evaluate the influence of the pharmacokinetic properties of fazadinium upon some pharmacodynamic parameters, such as the possible link between the twitch-height recovery rate and the plasma decay rate.

METHODS

Six healthy adults gave consent to the study. They were aged 35–75 yr, and were undergoing minor varicose vein surgery. None had any clinical or biochemical evidence of hepatic or renal damage.

One hour before anaesthesia, all the patients received diazepam 10 mg orally. Anaesthesia was induced with methohexitone 1 mg kg^{-1} and fentanyl 5 µg kg^{-1} i.v. When the patient was unconscious, ventilation of the lungs was controlled manually (circle system, 50% nitrous oxide in oxygen) until tracheal intubation, which was performed after the administration of fazadinium. Thereafter, the ventilation was controlled mechanically (circle system, 66% nitrous oxide) until the end of the surgical procedure. Ventilation was adjusted to achieve end-tidal carbon dioxide about 5.4 ± 0.1% (Datascope 500 CO_2 analyser) or arterial Pco$_2$ between 4.79 and 5.59 kPa (Corning 137). Supplementary doses of fentanyl were given when clinical signs of inadequate analgesia appeared. Heat loss from the body core and the exposed right arm was reduced by the use of a water-warming mattress with autoregulation (37 °C rectal temperature) and surgical sheets.

Before the start of anaesthesia, a displacement transducer (UC3 cell Statham), fitted with tension attenuator (UL4-20, Statham) and incorporated in a hand-grip, was secured with adhesive strips in

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the right hand of the patient to measure isometric thumb displacement (Sokoll, 1974). Two 25-gauge thin-walled needles were placed subcutaneously close to the ulnar nerve at the wrist, and mechanical activity of the adductor pollicis was induced by square-wave pulses lasting 0.2 ms and delivered at 0.1 Hz from a Grass S88 stimulator. The stimulation voltage equalled 1.5 times that required to evoke a maximal twitch response. The resulting analog signals were amplified and registered on a polygraph recorder. When a consistent control tension was achieved a bolus injection of fazadinium 0.75 mg kg^{-1} was administered.

Heparinized venous blood samples were obtained from the arm opposite the site of injection at 5, 10, 15, 20, 30, 60, 90, 120, 150, 180, 210 and 240 min after the start of injection of fazadinium; other samples were taken when appropriate to examine the plasma concentration of fazadinium corresponding to fixed degrees of paralysis. The total plasma concentrations of fazadinium were measured by a spectrofluorimetric method (Pastorino, 1978). In our laboratory this technique was found to be accurate to 0.05 μg ml^{-1} for fazadinium.

Plasma concentration profiles of fazadinium for each patient were fitted by a two-compartment open model simulation. The parameters of the model were calculated by iterative fitting and the computation procedures were performed using the SAAM 25 programme (Berman and Weiss, 1971) according to the diagram represented by figure 1 and the symbols defined in the appendix.

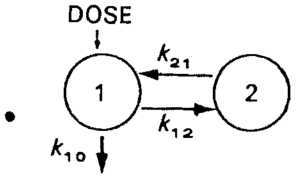

FIG. 1. Schematic representation of a two-compartment open model (see Appendix for definition of the illustrated symbols).

During recovery from paralysis when the responses were in the range 25–75%, the apparent mean rate of decline of the (log) plasma concentration ($K_{\mathrm{app}\,25-75}$) was determined according to the equation:

$$K_{\mathrm{app}\,25-75} = \frac{\log C_{25} - \log C_{75}}{t_{25} - t_{75}}$$

where C and t are the plasma concentrations and times respectively at 25 and 75% response levels.

The statistical analysis of the results was performed using linear regression and variance analysis. Significance was assigned at a level of 5% or less.

RESULTS

Table I summarizes the values of the calculated pharmacokinetic parameters in the patients. The mean values for this group of six healthy normal adults receiving fazadinium 0.75 mg kg^{-1} were (mean ± SEM): central compartment 9.78 ± 1.21 litre: peripheral compartment 9.80 ± 1.57 litre; k_{10} 0.0243 ± 0.0038 min^{-1}; k_{12} 0.0143 ± 0.0039 min^{-1}; k_{21} 0.0136 ± 0.0035 min^{-1}.

The metabolic clearance rate was 223 ± 24 ml min^{-1}. Calculated α and β half-lives were 15 ± 1 and 88 ± 8 min, respectively.

TABLE I. *Pharmacokinetic parameters: individual values (six patients). (For explanation of symbols see appendix)*

Patient no.	V_1 (litre)	V_2 (litre)	k_{10} (min^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})	MCR (ml min^{-1})	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)
1	9.05	7.32	0.0254	0.0144	0.0117	229	16	81
2	8.30	7.18	0.0222	0.0143	0.0124	184	18	93
3	7.00	8.98	0.0410	0.0181	0.0233	287	12	80
4	11.90	14.36	0.0248	0.0081	0.0097	296	18	126
5	7.68	6.09	0.0195	0.0300	0.0238	150	11	76
6	14.76	14.91	0.0130	0.0010	0.0010	192	15	70
Mean	9.78	9.80	0.0243	0.0143	0.0136	223	15	88
SEM	1.21	1.57	0.0038	0.0039	0.0035	24	1	8

TABLE II. *Individual values of the pharmacodynamic parameters and* $K_{app25-75}$, *the decline of plasma concentration for* TH_{25-75} *interval*

Patient no.	Time interval 0–TH_{50} (min)	Time interval TH_{25-75} (min)	Recovery rate TH_{25-75} (% min^{-1})	$K_{app25-75}$ (min^{-1})
1	48	26	1.92	−0.0251
2	52	27	1.85	−0.0219
3	32	14	3.57	−0.0382
4	42	22	2.27	−0.0286
5	49	24	2.08	−0.0210
6	57	34	1.47	−0.0149
Mean	47	25	2.19	0.0249
SEM	4	2	0.30	0.0032

The mean total plasma concentrations observed for 25, 50 and 75% of TH recovery were ($\mu g\,ml^{-1}$) 1.90±0.17, 1.44±0.18 and 1.08±0.12, respectively.

A significant correlation ($P<0.01$) was found between the log plasma concentration of fazadinium and the TH values during the recovery from paralysis. The time elapsed between administration of fazadinium and TH recovery to 50% of the initial value (0–TH_{50} time interval) was 47±4 min. TH_{25-75}, which represents the time elapsed from the 25% to the 75% value of TH during the recovery phase was 25±2 min; the twitch recovery rate during this period was 2.19±0.30% min^{-1}. The mean fazadinium plasma decay rate observed during the TH_{25-75} recovery period was $-0.0249 \pm 0.0032\,min^{-1}$ (for individual values see table II).

To test pharmacokinetic and pharmacodynamic inter-relationships, linear regressions were performed between the pharmacodynamic parameters TH_{25-75} and 0–TH_{50}, and some pharmacokinetic parameters linked to the rate of elimination of the drug: β half-life, metabolic clearance rate (MCR), k_{10} and $K_{app25-75}$.

Among the tested regressions, only the correlations concerning MCR, k_{10} and K_{app} reached significance (table III).

TABLE III. *Value of the linear regression correlation co-efficient* (r) *between pharmacodynamic and pharmacokinetic parameters.* *P<0.05; **P<0.01; ***P<0.001

	$T_{\frac{1}{2}}^{\beta}$	MCR	k_{10}	$K_{app25-75}$
Recovery rate TH_{25-75} (% min^{-1})	0.09 n.s.	0.64 n.s.	0.95 **	0.95 **
0–TH_{50} (min)	0.29 n.s.	−0.76 *	−0.94 **	−0.98 ***

DISCUSSION

The pharmacokinetic parameters obtained in this study for fazadinium 0.75 $mg\,kg^{-1}$ are similar to those previously reported by Duvaldestin and others (1978), for 1.5 $mg\,kg^{-1}$. $T_{\frac{1}{2}}^{\alpha}$ (12±2 min observed for the 1.5-$mg\,kg^{-1}$ series and 15±1 min noted for the 0.75-$mg\,kg^{-1}$ dose), $T_{\frac{1}{2}}^{\beta}$ (76±5 *v.* 88±8 min) and k_{10} (0.0215±0.0018 min^{-1} *v.* 0.0243±0.0038) are quite similar. The similarity of these pharmacokinetic parameters despite the difference in dosage strongly suggests that the pharmacokinetics of fazadinium are linear since they obey the superposition principle proposed by Thron (1974); fazadinium is probably eliminated by passive and non-saturable mechanisms.

The degree of paralysis obtained by us is in agreement with that previously reported by Camu and d'Hollander (1978) for doses of 0.5–1.0 $mg\,kg^{-1}$ of fazadinium. The dose of 0.75 $mg\,kg^{-1}$ used in this study provides a significant depression of TH to 5–10% of its initial value. Such a twitch-height depression can still be measured with reasonable accuracy and allowed us to follow simultaneously, during the whole study, the plasma concentration and the twitch height.

The results of the present study confirm that a relationship exists between the plasma concentration of fazadinium and the magnitude of neuromuscular blockade during the offset of paralysis, as has been shown previously for tubocurarine (Matteo, Spector and Horowitz, 1974) and pancuronium (Agoston et al., 1977). The rate of decay of the plasma concentration will influence the speed of recovery from paralysis as shown in table

III. These correlations indicate that a large part of the interindividual TH recovery variation has its origin in the interindividual rate of decay of the plasma concentration. According to the dose administered, the speed of recovery will be more or less dependent upon distribution or elimination processes, especially in the case of fazadinium because of its short onset of action. In our study, a moderate dose of fazadinium was administered (0.75 mg kg^{-1}) and TH recovery rate was influenced by both distribution and elimination processes. For a larger dose, the offset of paralysis will become predominantly dependent upon elimination phenomena. Thus the relationship between the TH recovery rate and dose (Walts and Dillon, 1968; Katz, 1971) appears likely to have a pharmacokinetic explanation. Another factor which might influence the rate of recovery from paralysis is the movement of the relaxant from the perisynaptic space to the general circulation. The dissociation of the relaxant from the receptor is too fast to influence the recovery rate appreciably (Sheridan and Lester, 1977). The transfer of the relaxant remains governed by the concentration gradient between the perisynaptic space and the plasma, despite repetitive antagonist and receptor bindings (Armstrong and Lester, 1979). Between these two spaces, a pseudo-equilibrium of the concentrations is more likely to occur during the late recovery phase as indicated by the model of Hull and others (1978).

It is tempting to calculate the concentration of relaxant present in the perisynaptic space for a fixed TH value and to compare it with the plasma concentration. The concentration in the perisynaptic space (B) can be calculated from the relationships, first between B, the dissociation constant K_B and the receptor occupancy ratio (y_B) and, second, between y_B and TH established by Waud and Waud (1975). Accordingly, for a TH value of 50%, the perisynaptic concentration should approach eight times the value of the dissociation constant K_B. For fazadinium, K_B determined *in vitro* was 0.377 µmol litre^{-1} (Waud, 1977). Extrapolation to the present study would result in a perisynaptic concentration of 3 µmol litre^{-1}(0.377 × 8), or 1.70 µg ml^{-1}.

According to the positive gradient existing between the perisynaptic space and the plasma concentrations at the offset of paralysis, the observed plasma concentration for TH$_{50}$ was slightly smaller: 1.44 µg ml^{-1}.

APPENDIX

DEFINITION OF PARAMETERS RELATED TO A TWO-COMPARTMENT OPEN MODEL

V_1 = apparent volume of central compartment (litre)
V_2 = apparent volume of peripheral compartment (litre)
k_{10} = elimination rate constant (min^{-1})
k_{21} = peripheral to central compartment exchange rate constant (min^{-1})
k_{12} = central to peripheral compartment exchange rate constant (min^{-1})
MCR = metabolic clearance rate (ml min^{-1})—the product of k_{10} and V_1— defined as that part of the central compartment space completely purged of the drug by unit of time (Brownell, Berman and Robertson, 1968).

The values of $T_{\frac{1}{2}}^{\alpha}$ and $T_{\frac{1}{2}}^{\beta}$ expressed in the results are derived from the values of α and β representing the exponents in the formula:

$$C_1 = Ae^{-\alpha t}+Be^{-\beta t}$$

where C_1 represents a bi-exponential concentration decay observed in the case of single administration of the drug in V_1 at zero time.

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RELATIONS ENTRE LA DECOMPOSITION DES CONCENTRATIONS DE FAZADINIUM DANS LE PLASMA ET LA RECUPERATION DE SES EFFETS DE BLOCAGE NEUROMUSCULAIRE

RESUME

On a fait des recherches sur la relation qui existe entre le temps nécessaire à la décomposition des concentrations de fazadinium dans le plasma et le blocage neuromusculaire, après administration par voie intraveineuse de 0,75 mg kg^{-1} de ce produit à six patients anaesthésiés. La pharmacocinétique de fazadinium a été analysée en se basant sur un modèle ouvert à deux compartiments. On a trouvé qu'il y avait une corrélation significative entre la concentration de fazadinium dans le plasma et les valeurs de la hauteur de la crispation (TH) pendant le temps nécessaire à la récupération des effets du blocage ($P < 0{,}001$). Les concentrations totales moyennes dans le plasma pour 25%, 50% et 75% de la récupération TH ont respectivement été de 1,90 ± 0,17; 1,44 ± 0,18 et 1,08 ± 0,12 µg ml^{-1}. Le temps écoulé entre l'administration de fazadinium et la récupération TH jusqu'à 50% (0–TH$_{50}$) et la période de récuperation (TH$_{25-75}$) a été respectivement de 47 ± 4 mn et de 25 ± 2 min. Le taux de décomposition du fazadinium dans le plasma pendant la période TH$_{25-75}$ ($K_{app\,25-75}$) a été de 0,0249 ± 0,0032 min^{-1}. Des corrélations significatives ($P < 0{,}01$) ont été observées entre la constante du taux d'élimination (k_{10}) du modèle pharmacocinétique, $K_{app\,25-75}$ ($P < 0{,}01$) et les paramètres pharmacodynamiques: intervalle de temps 0–TH$_{50}$ et taux de récupération TH$_{25-75}$. Ces résultats indiquent qu'une partie de la variation pharmacodynamique individuelle a son origine dans la variation pharmacocinétique interindividuelle.

BEZIEHUNG ZWISCHEN DER AUFLÖSUNG VON FAZADINIUM IM PLASMA UND DER ERHOLUNG AUS DEM NEUROMUSKULÄREN BLOCKIERUNGSEFFEKT DER DROGE

ZUSAMMENFASSUNG

Die Beziehung zwischen dem Zeitablauf der Zersetzung der Plasmakonzentration von Fazadinium und der neuromuskulären Blockierung wurde anlässlich der Verabreichung von 0,75 mg kg^{-1} auf intravenösem Weg an 6 narkotisierte Patienten. Die pharmakokinetischen Eigenschaften von Fazadinium wurden mittels eines offenen, zweiteiligen Modells analysiert. Man stellte eine signifikante Beziehung zwischen der Plasmakonzentration von Fazadinium und den Werten für Zuckungshöhe (TH) während der Erholung aus der Blockierung fest ($P < 0{,}001$). Die mittleren totalen Plasmakonzentrationen für eine TH-Erholung von 25, 50 und 75% waren: 1,90 ± 0,17; 1,44 ± 0,18; und 1,08 ± 0,12 µg ml^{-1}. Die jeweils zwischen Drogenverabreichung und der TH-Erholung auf 50% (0–TH$_{50}$), bezw. der Erholungsperiode TH$_{25-75}$ verstrichene Zeit betrug 47 ± 4 min und 25 ± 2 min. Die Plasma-Zerfallsrate von Fazadinium während der Periode TH$_{25-75}$ ($K_{app\,25-75}$) betrug: 0,0249 ± 0,0032 min^{-1}. Signifikante Beziehungen ($P < 0{,}01$) wurden beobachtet zwischen der Ausscheidungskonstanten (k_{10}) des pharmakokinetischen Modells, $K_{app25-75}$ ($P < 0{,}01$) und den pharmakodynamischen Parametern: 0–TH$_{50}$ Zeitintervall, und Erholungsrate TH$_{25-75}$. Diese Resultate zeigen, dass ein Teil der pharmakodynamischen Variation den Ursprung in den individuelle pharmakokinetischen Variationen hat.

RELACION ENTRE LA DISMINUCION DE LA CONCENTRACION DE FAZADINIO EN EL PLASMA Y LA RECUPERACION DE SU EFECTO DE BLOQUEO NEUROMUSCULAR

SUMARIO

Se investigó la relación entre la disminución progresiva, en el transcurso del tiempo, de la concentración de fazadinio en el plasma y el bloqueo neuromuscular, después de la administración intravenosa de 0,75 mg kg^{-1} a seis pacientes anestesiados. Se analizaron las farmacocinéticas del fazadinio con arreglo a un modelo de dos compartimientos. Se hayó una correlación significativa entre la concentración de fazadinio en

el plasma y los valores correspondientes a la altura de contracción (TH) desde el bloqueo ($P < 0{,}001$). Las concentraciones totales medias en el plasma, para recuperaciones del 25%, 50% y 75% de la TH fueron de: 1,90 ± 0,17; 1,44 ± 0,18 y de 1,08 ± 0,12 $\mu g\,ml^{-1}$ respectivamente. El tiempo transcurrido entre la administración del fazadinio y la recuperación TH al 50% ($O–TH_{50}$) y el periodo de recuperación TH_{25-75} fue de 47 ± 4 minutos y de 25 ± 2 minutos respectivamente. El régimen logarítmico de disminución de fazadinio en el plasma, durante el periodo TH_{25-75} ($K_{app\,25-75}$) fue de: 0,0249 ± 0,0032 min^{-1}. Se observaron correlaciones significativas ($P < 0{,}01$) entre la constante del régimen de eliminación (k_{10}) del modelo farmacocinético, $K_{app\,25-75}$ ($P < 0{,}01$) y los parámetros farmacocinéticos: Intervalo de tiempo $0–TH_{50}$ y el régimen de recuperación TH_{25-75}. Estos resultados mostraron que cierta parte de la variación farmacocinética individual tuvo su origen en la variación farmacocinética interindividual.

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EFFECT OF DIAZEPAM ON PANCURONIUM-INDUCED NEUROMUSCULAR BLOCKADE MAINTAINED BY A FEEDBACK SYSTEM

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SUMMARY

The possibility of an interaction between diazepam and pancuronium bromide was investigated in six patients undergoing general anaesthesia maintained with fentanyl, droperidol and nitrous oxide. Neuromuscular blockade was controlled using a feedback mechanism which automatically adjusted the rate of injection of pancuronium to maintain between 71.4 and 72.9% blockade. Diazepam 0.14 mg kg^{-1} i.v. produced blood concentrations within the therapeutic range, but did not produce consistent changes in the level of blockade, pancuronium concentration in the blood or pancuronium consumption measured over 20 min.

The possibility of interaction between diazepam and neuromuscular blockers was first suggested by Stovner and Endresen (1965) in a letter describing the advantages of diazepam as an induction agent for anaesthesia in man. They found that it did not potentiate the effects of tubocurarine or diallylnortoxiferine and similar conclusions were drawn by Dretchen, Ghonheim and Long (1971) from studies of tubocurarine, gallamine and decamethonium. The improvement of *in vivo* methods for measuring neuromuscular blockade, such as the train-of-four technique, led Bradshaw and Maddison (1979) to study diazepam 0.16 mg kg^{-1} with suxamethonium, tubocurarine, pancuronium, fazadinium and alcuronium. They concluded that there was no interaction.

The main evidence for an interaction between diazepam and a neuromuscular blocker comes from the work of Feldman and Crawley (1970) who found that diazepam increased the duration of action of gallamine, and decreased that of suxamethonium.

In studies of patients, drugs used as part of the anaesthetic technique may influence the neuromuscular junction and possibly obscure small changes produced by the test drug. Halothane and morphine, for example, have been found to possess neuromuscular blocking properties and have been used in some of the previous studies (Katz, 1971; Duke et al., 1979; Hughes and Payne, 1979). Other factors which may obscure an interaction include failure to maintain a stable acid–base state during the study and to achieve adequate blood concentrations of diazepam (Miller and Roderick, 1978). The patient's disease may cause changes in the distribution and elimination of drugs and it is important to confirm that following an appropriate dose i.v., a therapeutic concentration of diazepam is achieved.

This study was undertaken to examine the possibility of interaction between diazepam and pancuronium by providing a controlled pharmacological environment of steady neuromuscular blockade maintained by feedback control.

METHOD

Patients

Six healthy patients presenting for routine general surgery were studied. Patients with known neuromuscular disease or receiving drugs known to influence neuromuscular function were excluded. Results of biochemical investigations were normal. All patients gave informed consent. The patients received no premedication apart from aluminium hydroxide (Aludrox) 30 ml given orally 1 h before anaesthesia.

Anaesthetic technique

Anaesthesia was induced using methohexitone 1.0 mg kg^{-1} and endotracheal intubation facilitated with suxamethonium 1.0 mg kg^{-1}. Nitrous

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oxide was used to maintain anaesthesia and doses of fentanyl 5.0 $\mu g\,kg^{-1}$ and droperidol 0.14 $mg\,kg^{-1}$ were injected over 1 min both to facilitate automatic ventilation and to obtain baseline electromyogram (e.m.g.) measurements. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.0% measured with a "Datex" carbon dioxide analyser. Cannulae were inserted to both arms for i.v. infusions and blood sampling. Further doses of fentanyl and droperidol were given during the anaesthetic according to the requirements of the patient. E.c.g. was monitored throughout the operation, and arterial pressure was measured using an oscillotonometer. If infusion of stored blood was necessary during the study period, the experiment was abandoned, as the addition of more binding sites from blood protein may have altered the feedback control system.

Feedback control system

The method of controlling neuromuscular blockade by a feedback system has already been described (Asbury, Brown and Linkens, 1980; Brown et al., 1980). The method involves supramaximal stimulation (0.1 Hz) of the ulnar nerve at the elbow and recording the resultant e.m.g. developed in the muscles of the hand. The e.m.g. is then rectified and integrated to give a voltage (RIe.m.g.) and compared with a reference voltage set to represent 80% blockade. The voltage difference is used to drive a small peristaltic pump which delivers pancuronium (1 mg in 20 ml) to the patient. The pancuronium is diluted with saline in a sterile infusion burette (Travenol) and the change in volume per unit time gives an indication of the consumption. The RIe.m.g., which is the indicator of the level of blockade, is recorded using a pen recorder and by hand from readings on a digital voltmeter.

In each case, as the levels of blockade were steady before and after diazepam administration, the mean and standard deviations were calculated from measurements of the RIe.m.g. trace sampled at 5-min intervals.

Diazepam administration

When a stable neuromuscular blockade had been achieved, the consumption of pancuronium over 20 min was calculated from the changes in burette readings. Venous blood samples were drawn without a tourniquet at 5-min intervals from a cannula for estimation of pancuronium concentration.

After 20 min of stable blockade, diazepam 0.14 $mg\,kg^{-1}$ was injected to a peripheral vein over 1 min and flushed in with 10 ml isotonic saline. Recordings were continued as before, and further blood samples were drawn at 5-min intervals for pancuronium and diazepam estimations.

Estimations of pancuronium and diazepam concentrations

Pancuronium concentrations were measured to a sensitivity of 0.02 $\mu g\,ml^{-1}$ using the fluorimeter technique developed by Kersten, Meijer and Agoston (1973).

Diazepam concentrations were measured to a sensitivity of 3 $ng\,ml^{-1}$ using a gas chromatographic technique with electron capture detection described by Greenblatt (1978).

Statistical analysis

Student's t test was used to estimate the significance of differences in levels of neuromuscular blockade and blood concentrations with each patient acting as his own control. The nature of the experiment precluded randomizing the order of the test periods.

The consumptions can be treated as a series of pairs and the paired t test was used to calculate the level of significance.

RESULTS

The patients as a group (table I) were younger and lighter than is usual for general surgical patients.

Before diazepam was given (table II), the levels of blockade expressed as a percentage of the base line readings in the unblocked state, ranged from 71.4 to 72.9% The offset, the difference between the desired level of blockade (80% of baseline) and that actually obtained, was up to 8.6% and is compatible with that observed in previous studies. The standard deviations of the levels of blockade are small, suggesting that the feedback system maintained a steady state. The worst coefficient of variation was 3.3%.

After administration of diazepam (table II), the system was still under feedback control as mean levels of blockade similar to those before the diazepam were achieved; the worst coefficient of variation was 3.6%. In one case, there was a significant difference between the mean level of blockade before and after the diazepam.

TABLE I. *Details of operations and patients*

	Weight (kg)	Age (yr)	Operation
	66	43	Right hemicolectomy
	56	16	Highly selective vagotomy
	76	63	Cholecystectomy
	56	66	Roux-en-Y
	71	20	Highly selective vagotomy
	47	27	Pan procto-colectomy
Mean	62.0	39.2	

TABLE II. *Levels of neuromuscular blockade before and after the injection of diazepam 0.14 mg kg*$^{-1}$ *i.v. n.s. = non-significant difference*

Degree of blockade before diazepam		Degree of blockade after diazepam		
Mean	SD	Mean	SD	Significance
71.4	1.5	69.9	1.0	n.s.
72.9	0.9	73.2	1.5	n.s.
72.4	2.6	73.8	0.5	n.s.
71.8	2.4	74.2	2.5	n.s.
71.6	0.8	69.6	1.3	$P<0.05$
72.2	1.8	72.4	1.2	n.s.

TABLE III. *Changes in pancuronium concentrations before and after diazepam 0.14 mg kg*$^{-1}$

Pancuronium concn before diazepam (µg ml^{-1})		Pancuronium concn after diazepam (µg ml^{-1})		
Mean	SD	Mean	SD	Significance
0.17	0.03	0.15	0.05	n.s.
0.13	0.01	0.16	0.02	$P<0.01$
0.14	0.04	0.14	0.01	n.s.
0.23	0.01	0.23	0.01	n.s.
0.09	0.01	0.15	0.02	$P<0.01$
0.22	0.02	0.18	0.01	$P<0.01$

TABLE IV. *Changes in pancuronium consumption before and after diazepam 0.14 mg kg*$^{-1}$. *The differences are not significant*

Pancuronium consumption (µg kg^{-1} min^{-1})	
Before diazepam	After diazepam
0.53	0.72
0.53	0.53
0.50	0.30
0.49	0.36
0.49	0.70
0.48	0.43

TABLE V. *Diazepam concentrations after i.v. bolus of 0.14 mg kg*$^{-1}$

Diazepam concentration (ng ml^{-1})				
5 min	10 min	15 min	20 min	25 min
307	165	132	135	120
310	235	230	215	200
390	280	200	217	145
535	405	262	292	222
352	212	180	138	138
349	281	226	182	140

The mean blood concentrations of pancuronium (table III) before and after the diazepam were in the same therapeutic range and in three patients there was a significant change in the mean blood concentration, one patient showing a decrease.

The changes in pancuronium consumption before and after the diazepam were not significant (table IV).

Diazepam concentrations following the 0.14 mg kg^{-1} dose (table V) showed the expected exponential decay, with concentrations in the therapeutic range (Greenblatt, 1978).

DISCUSSION

One of the reasons for embarking upon this study was that, with the aid of feedback control of neuromuscular blockade, it is now possible to maintain a stable pharmacological environment which gives the best chance of detecting interactions between pancuronium and diazepam. This approach necessarily places considerable reliance on the accuracy of the feedback control and emphasizes the basic assumption implicit in this study that, once under stable feedback control, the level of blockade and the consumption of pancuronium will remain steady, unless disturbed—for example by diazepam. The assumption that blockade and consumption remain stable has already been tested in patients by the authors and found to be true for periods up to 2 h.

If diazepam transiently potentiated the effect of pancuronium, rapid increase in blockade would occur followed by a gradual reduction to the original level of blockade. If the effect of the diazepam was prolonged, for example for 20 min, then a long-term change in offset would occur. Corresponding changes would also occur in the consumption and in blood concentrations of pancuronium.

There was a significant change in the mean level of blockade only once, and this was a decrease in blockade instead of the expected increase.

The changes in blood concentration of pancuronium showed no consistent pattern. Although significant ($P < 0.01$) changes occurred in two patients, the concentration increased when a decrease would have been expected. The changes in pancuronium consumption were equally unimpressive.

Thus there is no consistent evidence that diazepam interacts with pancuronium within the limitations of the experiment. This finding is in agreement with the conclusions of Bradshaw and Maddison (1979).

A negative result is always more difficult to prove than a positive one and therefore it is important to be aware of the limitations of this study. One is that the control might not have been stable enough and a fleeting effect of diazepam could be lost within the oscillations produced by the control system. This is unlikely, however, as the standard deviations of the levels of blockade are all small, suggesting close control.

Another possibility is that the concentrations of diazepam were insufficient to show the interaction effect. However, concentrations of diazepam achieved during this experiment compare favourably with those in other studies (Greenblatt, 1978) and are similar to those found clinically. We suggest that if these blood concentrations do not cause an interaction and a true interaction really exists, then it is probably unimportant in clinical anaesthesia and can usually be ignored.

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EFFET DU DIAZEPAM SUR LE BLOCAGE NEUROMUSCULAIRE PROVOQUE PAR LE PANCURONIUM ET ENTRETENU PAR UN SYSTEME DE RETROACTION

RESUME

Nous avons fait des recherches sur la possibilité qui existe d'une interaction entre le diazépam et le bromure de pancuronium sur six patients soumis à une anesthésie générale, entretenue à l'aide de fentanyl, de dropéridol et de protoxyde d'azote. Le blocage neuromusculaire a été contrôlé à l'aide d'un mécanisme de rétroaction qui ajuste automatiquement le taux d'injection du pancuronium afin de maintenir le blocage entre 71,4% et 72,9%. Le diazépam administré par voie intraveineuse à raison de 0,14 mg kg^{-1} a produit des concentrations dans le sang se situant dans la plage thérapeutique, mais il n'a produit aucune variation constante dans le niveau du blocage; les concentrations de pancuronium dans le sang ou la consommation de pancuronium ont été mesurées pendant 20 min.

DIE WIRKUNG VON DIAZEPAM AUF EINE DURCH PANCURONIUM EINGELEITETE NEUROMUSKULÄRE BLOCKIERUNG, AUFRECHTERHALTEN DURCH EINE FEED-BACK-ANLAGE

ZUSAMMENFASSUNG

Die Möglichkeit einer Wechselwirkung zwischen Diazepam und Pancuroniumbromid wurde an 6 Patienten untersucht, die einer allgemeinen Narkose mit Fentanyl, Droperidol und Stickoxyd unterzogen wurden. Die neuromuskuläre Blockierung wurde mittels eines Feed-back-Mechanismus' kontrolliert, der die Zuführungsrate von Pancuronium automatisch so regelte, dass eine Blockierung zwischen 71,4 und

72,9% aufrechterhalten wurde. Diazepam 0,14 mg kg^{-1}, intravenös gegeben, bewirkte Blutkonzentrationen innerhalb des therapeutischen Bereiches, aber keine konsistenten Veränderungen der Blockierungsstärke, der Blutkonzentration von Pancuronium oder des Pancuronium-Verbrauchs gemessen innerhalb von 20 Minuten.

EFECTO DEL DIAZEPAM EN EL BLOQUEO NEUROMUSCULAR INDUCIDO POR PANCURONIO Y MANTENIDO POR UN SISTEMA DE RETROALIMENTACION

SUMARIO

Se investigó en seis pacientas sometidos a anestesia general mantenida con fetanil, droperidol y óxido nitroso, la posibilidad de una interacción entre el diazepam y el bromuro de pancuronio. El bloqueo neuromuscular se controló usando un mecanismo de retroalimentación que ajustaba automáticamente el régimen de inyección del pancuronio para mantener un bloqueo de entre 71,4% y 72,9%. Diazepam 0,14 mg kg^{-1} intravenoso produjeron concentraciones sanguineas comprendidas dentro de la gama terapéutica, pero no produjeron concentraciones de pancuronio en la sangre ni una reducción de éste a lo largo de los 20 minutos de medición.

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USE OF 4-AMINOPYRIDINE TO REVERSE MORPHINE-INDUCED RESPIRATORY DEPRESSION IN MAN

R. L. SIA AND D. F. ZANDSTRA

SUMMARY

4-Aminopyridine administered to patients antagonized respiratory depression by morphine 0.33 mg kg^{-1}. It is suggested that 4-AP may be useful in the treatment of morphine-induced respiratory depression.

Morphine, when used to supplement anaesthesia has minimal effects on the cardiovascular system (Hasbrouck, 1971; Wong et al., 1973). However, in high dosage it can cause respiratory depression and somnolence which may persist for several hours (Hasbrouck, 1970; Longnecker, Grazis and Eggers, 1973; Gairola, Gupta and Pandley, 1980). Although such depression of respiration may not be a problem during operation when ventilation is controlled, it may be dangerous in the period after operation. 4-Aminopyridine increases the extracellular concentration of acetylcholine centrally and peripherally by enhancing transmitter release (Lundh, 1978), and has been found to stimulate breathing in anaesthetized cats (Fastier and McDowall, 1958; Folgering, Rutten and Agoston, 1979). In man it was shown that 4-aminopyridine (4-AP) can reverse fentanyl-induced respiratory depression (Sia et al., 1979). The present study was designed to confirm this finding in patients receiving morphine.

PATIENTS AND METHODS

Twenty patients, 14 male and six female, aged between 18 and 54 yr (mean 34 yr) were admitted for elective ear, nose and throat operations. All gave their full informed consent, and were free from respiratory disease. The study was performed before the commencement of surgery. Premedication consisted of droperidol 0.05 mg kg^{-1} and atropine 0.5 mg 1 h before operation. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and maintained with 67% nitrous oxide in oxygen. Suxamethonium 1 mg kg^{-1} was administered to facilitate orotracheal intubation and ventilation was controlled until spontaneous respiration reappeared. No further neuromuscular blocking agent was used. Whenever the patient showed signs of wakening, thiopentone 25–50 mg was administered to maintain stable anaesthesia.

A radial artery cannula was inserted after the induction of anaesthesia to allow withdrawal of arterial blood for the measurement of blood-gas tensions. End-expiratory carbon dioxide concentration was monitored using a Godardt infra-red capnograph. Respiratory flow, tidal volume and changes in the frequency of respiration were recorded by means of a No. 2 Fleisch flow transducer connected to the pneumotachograph. Tidal volume and respiratory rate were measured with a Wright respirometer. Occlusion pressures were read by digital display (Hewlett Packard ECG apparatus) and were measured by a Statham P23 ID pressure transducer as described by Kay (1979). Control values were measured over a 1 min period with the patient breathing 67% nitrous oxide in oxygen. A bolus dose of morphine sulphate 0.33 mg kg^{-1} was injected i.v. over a period of 10 s. This resulted in a period of apnoea during which the lungs were ventilated manually at a rate sufficient to keep the end-tidal carbon dioxide concentration between 5% and 7%. As soon as depressed spontaneous breathing appeared, two consecutive series of measurements, 2 min apart, of respiratory flow, tidal volume, respiratory rate, occlusion pressure and arterial $P\text{CO}_2$ and $P\text{O}_2$ were made. A bolus of 4-AP 0.3 mg kg^{-1} was injected over a period of 10 s and 2 min later the same two consecutive series of measurements, 2 min, apart were made. The same sequence of measurements was undertaken in a group of control patients to whom 4-AP 0.3 mg kg^{-1} alone was given. No data

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on the use of morphine alone are presented because prolonged respiratory depression is known to occur after substantial amounts of morphine (Longnecker, Grazis and Eggers, 1973; Johnstone, 1975). Statistical analysis of the results was by means of the paired one-tailed Student's *t* test.

RESULTS

All patients ($n = 16$) who received morphine became apnoeic, following which respiration was slow and shallow. After the administration of 4-AP, there was a statistically significant improvement in all the indices measured. The following changes were observed:

(1) Reversal of respiratory depression was evident 30 s after 4-AP as shown by the pneumotachograph (fig. 1).

(2) The tidal volume more than doubled and approached the control value (fig. 2B).

(3) There was a significant increase in respiratory frequency (fig. 2C).

(4) There was a significant increase in the occlusion pressure (fig. 2D).

(5) There was a decrease in $P\mathrm{CO}_2$, whereas $P\mathrm{O}_2$ remained greater than its physiological value (figs 2A, 2E).

(6) In the control group of patients ($n = 4$) who received 4-AP alone, no significant changes were seen in tidal volume, respiratory rate, $p^{\circ}_{\max}$, $P\mathrm{CO}_2$ or $P\mathrm{O}_2$ (fig. 3).

DISCUSSION

The administration of 4-AP 0.3 mg kg^{-1} to patients with morphine-induced respiratory depression significantly improved tidal volume, respiratory rate, $P\mathrm{CO}_2$ and occlusion pressure. The occlusion pressure ($p^{\circ}_{\max}$) has been found to be a reliable index of respiratory drive in anaesthetized

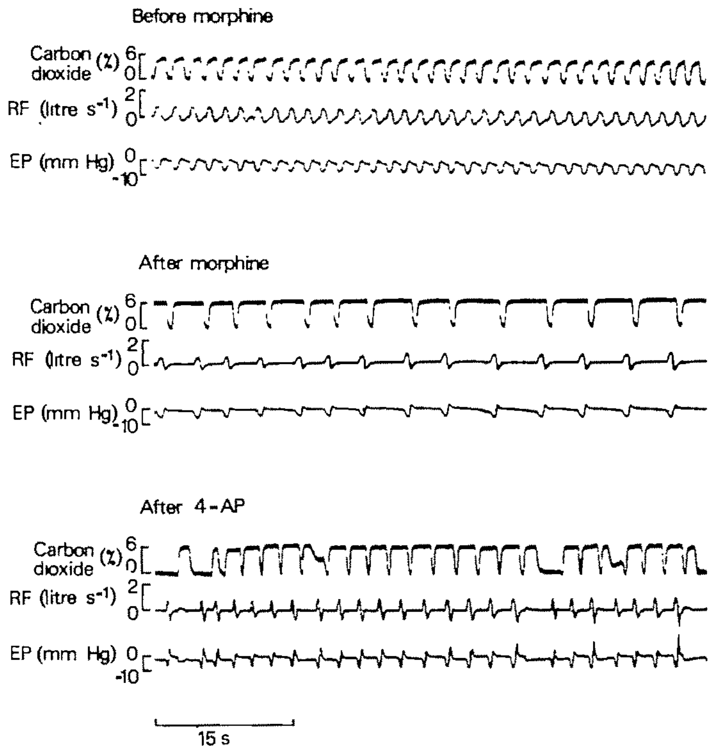

FIG. 1. Effect of 4-AP on morphine-induced depression of respiration. Simultaneous recordings of expired carbon dioxide concentration, respiratory flow (RF) and endotracheal pressure (EP) in a patient breathing 67% nitrous oxide in oxygen. Before morphine = control recordings after tracheal intubation; after morphine = tracing obtained 30 s after administration of morphine 0.33 mg kg^{-1}; after 4-AP = subsequent tracing obtained 2 min after morphine injection and 30 s after 4-AP 0.3 mg kg^{-1} i.v.

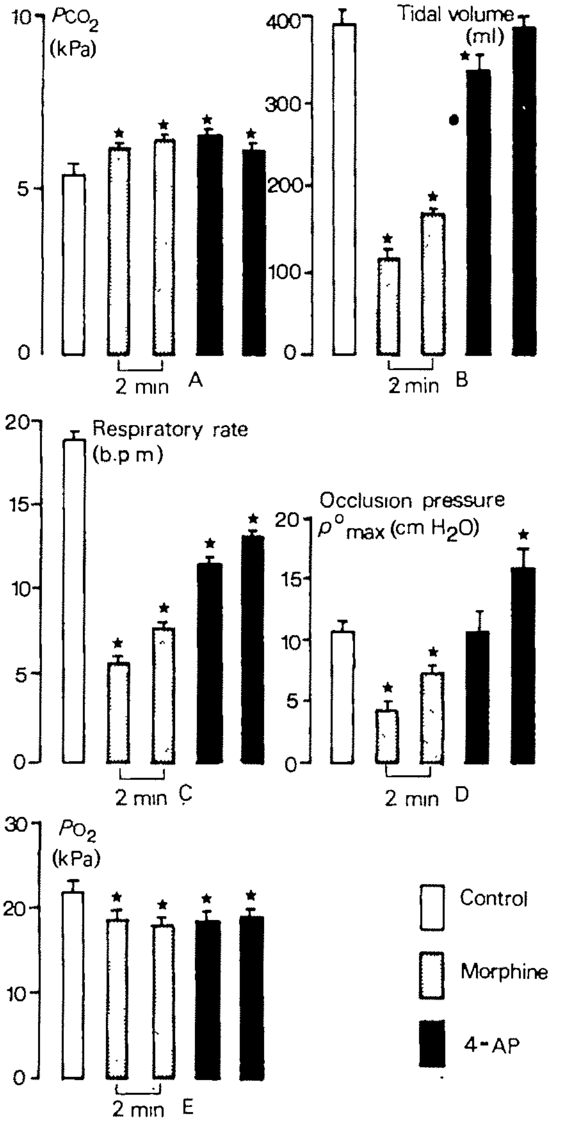

FIG. 2. Effect of 4-AP 0.3 mg kg^{-1} on respiration in patients breathing spontaneously 67% nitrous oxide in oxygen before surgery. Open histograms represent mean control values obtained after 1 min of spontaneous respiration. Dotted histograms represent mean values obtained after injection of morphine at 2-min intervals. Closed histograms represent mean values obtained at 2-min intervals after 4-AP. Vertical lines are SEM. $*P<0.01$; paired Student's t test. $n = 16$.

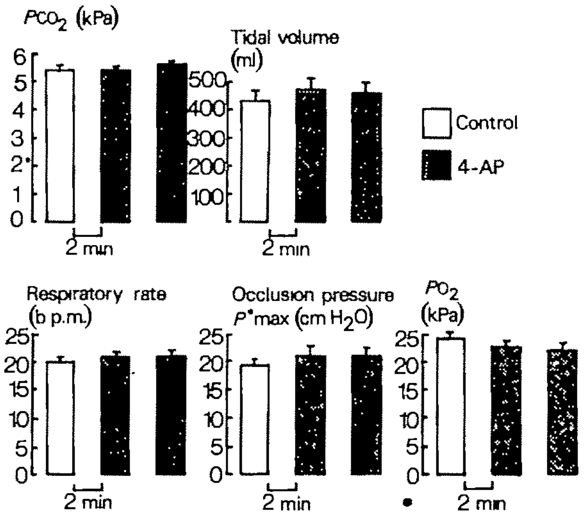

FIG. 3. Effect of 4-AP 0.3 mg kg^{-1} alone in the absence of morphine in patients breathing spontaneously 67% nitrous oxide in oxygen before surgery. Detailed description of the histogram is given in legend to figure 2. No changes were statistically significant (Student's t test). $n = 4$.

man (Derenne et al., 1976). During the period of depressed respiration following the administration of morphine, $p°_{max}$ was extremely low and reflected probably the inhibition of respiratory drive. The significant increase in $p°_{max}$ which occurred after 4-AP may indicate that 4-AP only stimulates respiratory centre activity when this is depressed markedly. In the group of patients who received 4-AP alone, the drug did not appear to produce any significant changes.

Recent investigations suggest that calcium plays an important role in the interaction of opiates with neuronal tissue. The acute administration of morphine was found to decrease the concentration of calcium in the brain, in particular in nerve endings (Yamamoto et al., 1978). An *in vitro* study on longitudinal muscle strips of guineapig ileum showed that an increase in calcium concentration completely reversed the effects of morphine (Opmeer and van Ree, 1979). Since 4-AP blocks the potassium channels and increases the influx of calcium into the nerve terminals (Lundh, 1978), it appears that one of the possible mechanisms of action of 4-AP in the reversal of morphine-induced respiratory depression may be by increasing calcium concentrations in the brain. 4-AP 0.3 mg kg^{-1} given i.v. to conscious volunteers caused aching pain around the site of injection lasting for about 20 min and perioral paresthesia lasting for about 5 min. It seems that 0.3–0.35 mg kg^{-1} is a safe and effective dose to antagonize morphine-induced respiratory depression in man without producing side-effects such as restlessness and convulsive activity (Spyker et al., 1980).

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USAGE DE LA 4-AMINOPYRIDINE POUR INVERSER LES DEPRESSIONS RESPIRATOIRES PROVOQUEES CHEZ L'HOMME PAR LA MORPHINE

RESUME

L'administration de 4-aminopyridine à des malades a contrarié la dépression respiratoire causée par 0,33 mg kg^{-1} de morphine. On suggère dans cet article que 4-AP pourrait être utile pour le traitement de toute dépression respiratoire provoquée par la morphine.

VERWENDUNG VON 4-AMINOPYRIDIN ZUR AUFHEBUNG VON MORPHIUMBEDINGTER RESPIRATORISCHER DEPRESSION BEIM MENSCHEN

ZUSAMMENFASSUNG

Die Verabreichung von 4-Aminopyridin führte zur Aufhebung einer durch 0,33 mg kg Morphium bedingten respiratorischen Dämpfung, woraus geschlossen wird, dass diese Droge 4-AP zu diesem Zweck auf nutzbringende Weise eingesetzt werden kann.

USO DE 4-AMINOPIRIDINA PARA INVERTIR LA DEPRESION RESPIRATORIA INDUCIDA MEDIANTE MORFINA EN EL HOMBRE

SUMARIO

La 4-aminopiridina administrada a pacientes invirtió la depresión respiratoria inducida por 0,33 mg kg^{-1} de morfina. Se sugiere que la 4-AP puede usarse provechosamente en el tratamiento de la depresión respiratoria inducida por la morfina.

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SINGLE AND COMBINED EFFECTS OF ATROPINE AND METOCLOPRAMIDE ON THE LOWER OESOPHAGEAL SPHINCTER PRESSURE

B. R. COTTON AND G. SMITH

SUMMARY

The effects of atropine and metoclopramide on the lower oesophageal sphincter pressure (LOSP) were studied in 12 healthy volunteers using oesophageal pressure transducers. Atropine decreased LOSP significantly at 5 min after i.v. injection ($P<0.005$) and this change was sustained for 60 min. Metoclopramide increased LOSP significantly at 3 min after administration i.v. ($P<0.05$) and this change was sustained for 40 min. Following consecutive administration of the drugs the effects of atropine predominated.

At the lower end of the oesophagus is a region of increased intraluminal pressure termed the lower oesophageal sphincter (LOS) or high pressure zone (HPZ). Although this region is not anatomically distinct, its position may be identified and tone quantified by oesophageal manometry. The lower oesophageal sphincter is thought to be an important mechanism in the prevention of reflux of gastric contents into the oesophagus and therefore there has been considerable interest recently in changes in LOS magnitude produced by drugs encountered during anaesthetic practice.

TABLE I. *Effect of atropine (A) and metoclopramide (M) on barrier pressure (BP)*

Year	Author	Drug	BP	Timing
1968	Skinner and Camp	A	Decrease	After at least 5 min
1976	Brock-Utne and others	A	Decrease	None made
		M	Increase	None made
		A+M	No change	None made
1977	Brock-Utne and others	A	Decrease	None made
1978	Laitinen and others (anaesthetized dogs)	A	Decrease	None made
		M	Increase	None made
		Consecutive A+M	No increase following initial decrease	None made
		Consecutive M+A	No decrease following initial increase	None made

It is generally assumed that tendency to regurgitation may be related to the barrier pressure (BP), which is the difference in pressure between the gastric and the high pressure zone. Although all previous studies suggest that atropine decreases and metoclopramide increases BP (table I), only one study of the simultaneous administration of atropine and metoclopramide showed that there was no change in LOS pressure (Brock-Utne et al., 1976). In addition, it has been shown in anaesthetized dogs that the random consecutive administration of atropine and metoclopramide with a 5-min interval produced no alteration in BP from the change produced by the first drug (Laitinen et al., 1978). However, in all these studies there was no indication of the timing of the single measurement

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which was made following the i.v. injections of the drugs and no assessment of the time-course or duration of effects. The purpose of this study was to define the onset and duration of action of atropine and metoclopramide following both their single and consecutive administrations in man.

METHODS

Twelve healthy volunteers (ages 21–38 yr) with no history of gastrointestinal, respiratory or cardiovascular disease, and not receiving any drug therapy, gave informed consent to take part in this study. Eight subjects were male and, of the total, five were smokers. All subjects had fasted and, where relevant, refrained from smoking for at least 6 h before swallowing a silastic nasogastric tube (3 mm o.d.) into which were embedded three subminiature strain gauge pressure transducers situated laterally at 5, 10 and 15 cm from the distal tip (Gaeltec Ltd). This was connected via a pre-amplifier to a chart recorder (Linearcorder Mk III). Each transducer was calibrated by immersion in a column of water at 37 °C. Preliminary assessment of the performance of the transducers revealed negligible drift in calibration with a 2 °C variation in temperature and an insignificant drift in calibration or zero baseline over a period of 60–90 min.

The tube was swallowed orally until all the transducers were in the stomach and a period of 15–20 min was allowed to elapse to enable gastric hyperactivity to diminish.

Control measurements of gastric (GP) and HPZ pressures were then made by withdrawal of the tube from the stomach in increments of 0.5 cm with pauses of a few seconds, through the HPZ until all the transducers were in the oesophagus. The proximal transducer enabled pressure changes produced by swallowing to be recognized from the oesophageal tracing as described previously (Smith, Dalling and Williams, 1978). When swallowing occurred, all measurement was discarded and the pull-through manoeuvre was repeated. All measurements were related to the end-expiratory point.

Each volunteer swallowed the tube on three separate occasions. On the first occasion, the subject received atropine 0.6 mg i.v. or meto-

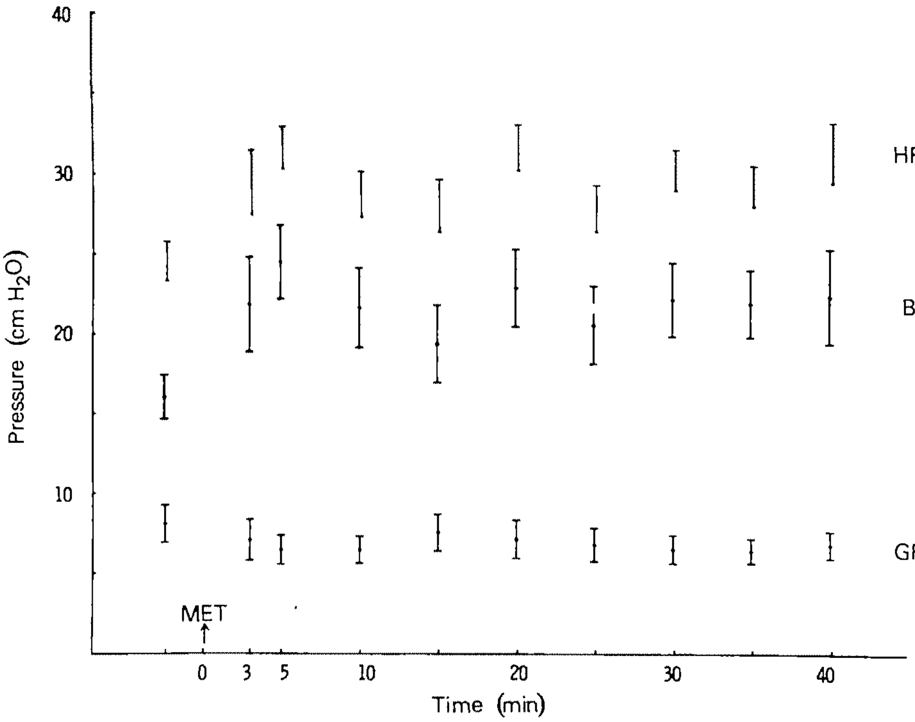

FIG. 1. Effect of metoclopramide 10 mg (MET) i.v. gastric (GP), barrier (BP) and lower oesophageal sphincter (HPZ) pressures in healthy volunteers (mean ± SEM except for HPZ when only mean + SEM shown. $n = 12$).

clopramide 10 mg i.v. The order of administration was randomized between subjects. On the second occasion each received the second drug. On the third occasion six of the volunteers received atropine 0.6 mg followed 10 min later by metoclopramide 10 mg; the other six volunteers received the drugs in reverse order. Measurements were made at 3 min, 5 min and then 5-min intervals following the i.v. injections of the drugs until the end of recording at 60 min for atropine, 40 min for metoclopramide and 50 min for the consecutive administration study. At the end of recording, the tube was removed and the zero baseline and calibration were re-assessed.

All results were analysed using Student's *t* tests for paired data.

RESULTS

Metoclopramide produced an increase in BP from 16.1 ± 1.4 (mean ± SEM) to a maximum at 5 min after injection of 24.8 ± 2.3 cm H_2O ($P<0.005$). Thereafter barrier pressure remained increased significantly until the end of recording at 40 min post-injection (fig. 1). It may be seen from figure 1 that significant increases in BP and HPZ pressure were apparent 3 min after injection.

In contrast, atropine decreased BP from 18.8 ± 1.4 cm H_2O to 13.5 ± 1.4 cm H_2O ($P<0.01$) and the pressure remained decreased significantly until the end of recording at 60 min. However, at 55 and 60 min this decrease in BP resulted from a significant increase in GP ($P<0.005$) rather than a decrease in HPZ pressure. Again, the effect of atropine was evident when the first measurement was made 3 min after injection (fig. 2).

When both drugs were given consecutively, BP decreased significantly from 16.9 ± 2.3 cm H_2O to 10.5 ± 1.5 cm H_2O ($P<0.05$) (in those who received atropine first). However, following the injection of metoclopramide, BP did not increase significantly above the values to which it had decreased following atropine (fig. 3). These changes were sustained until the end of recording at 50 min, apart from the measurement at 35 min, when BP approximated to control values.

For the subjects who received metoclopramide first (fig. 4), BP increased from 21.7 ± 2.8 cm H_2O to 27 ± 1.8 cm H_2O. However, following the in-

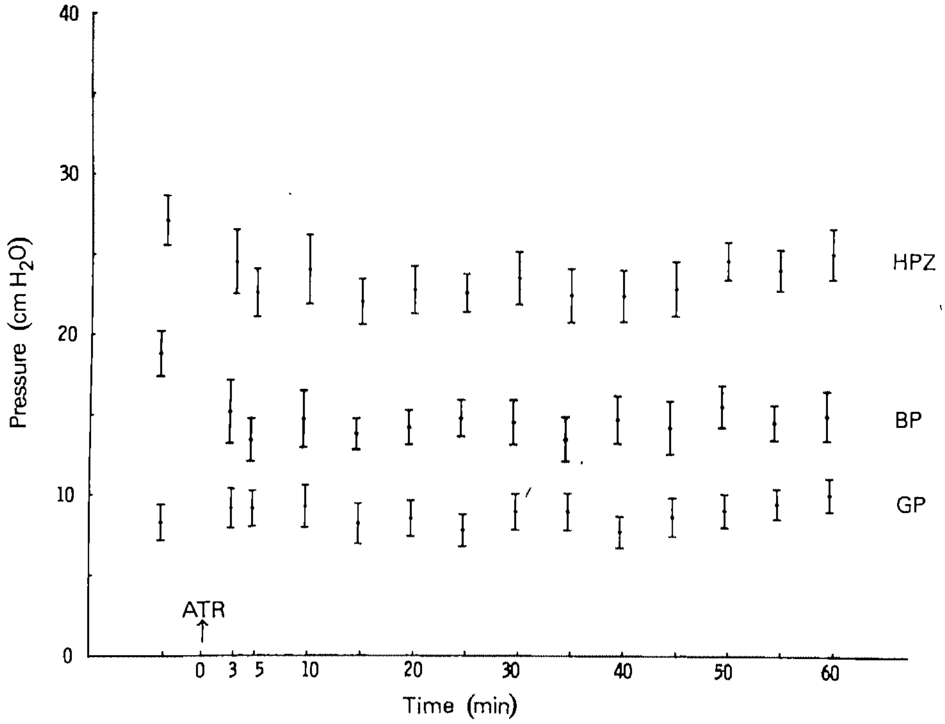

FIG. 2. Effect of atropine 0.6 mg (ATR) i.v. on gastric (GP), barrier (BP) and lower oesophageal sphincter (HPZ) pressures in healthy volunteers (mean ± SEM. $n = 12$).

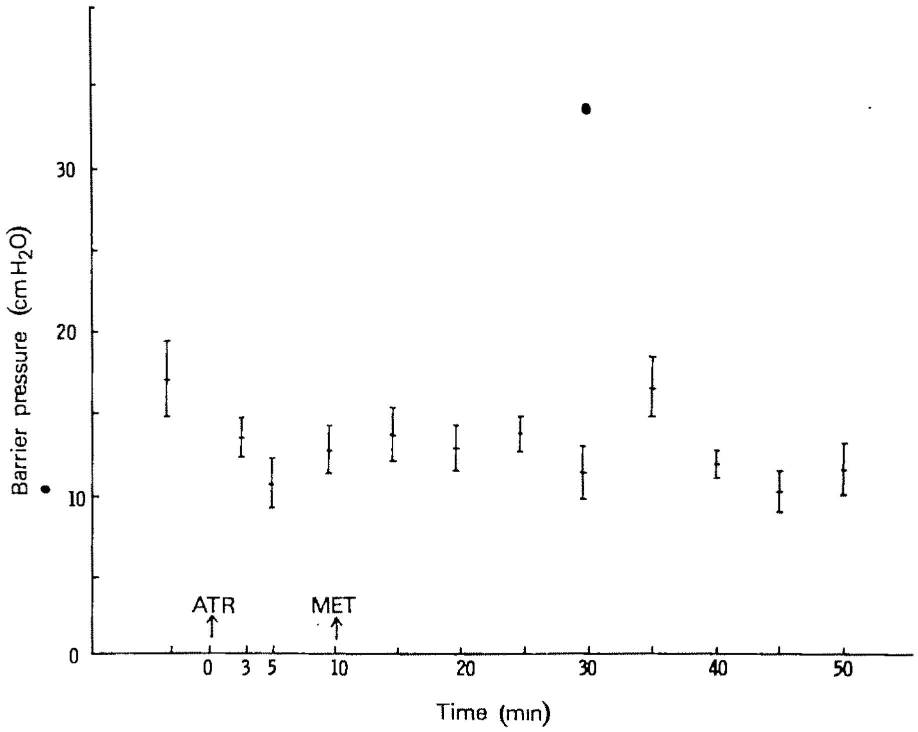

FIG. 3. Effect of atropine 0.6 mg (ATR) i.v. followed 40 min later by metoclopramide (MET) 10 mg i.v. on barrier pressure (HPZ minus gastric pressure) (mean ± SEM. $n = 6$).

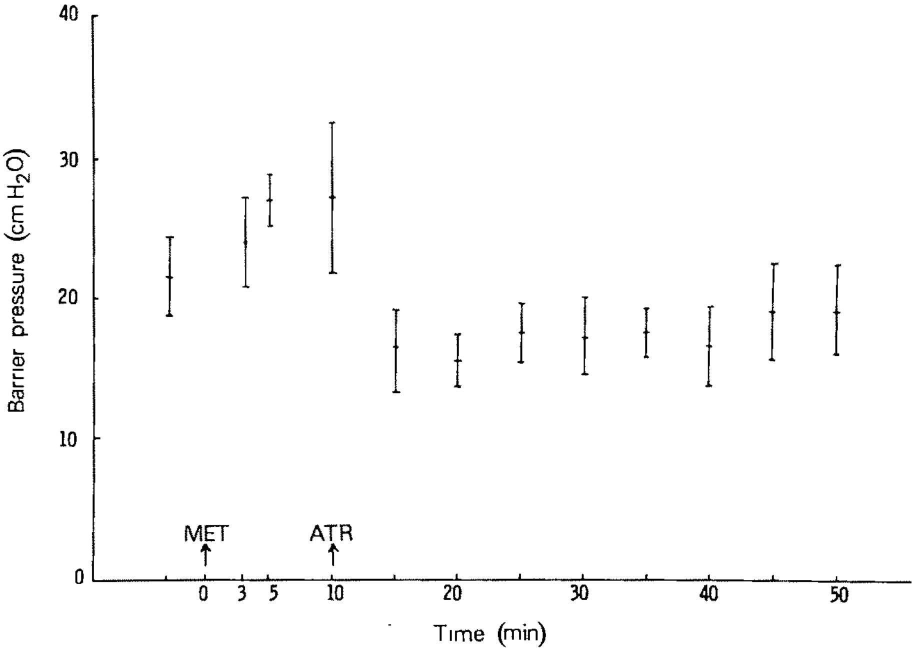

FIG. 4. Effect of metoclopramide (MET) 10 mg i.v. followed 10 min later by atropine (ATR) 0.6 mg i.v. on barrier pressure (HPZ minus gastric pressure) (mean ± SEM. $n = 6$).

jection of atropine, BP decreased to 16.3 ± 2.9 cm H_2O, a value not only significantly different from that to which it had increased ($P < 0.025$), but also less than control ($P < 0.05$). These changes were sustained until the end of recording at 50 min (fig. 4).

DISCUSSION

This study confirms previous observations that, when given independently, atropine decreases and metoclopramide increases BP (Skinner and Camp, 1968; Brock-Utne et al., 1976, 1977; Laitinen et al., 1978). Although the extent of the decrease following atropine is comparable to that noted in previous studies, it is not possible to make strict comparisons. It is well recognized that different types of measuring system record different pressures in the LOS region.

We noted that following atropine, BP decreased significantly by 3 min after injection and this decrease persisted for 60 min. However, inspection of figure 2 reveals that there appeared to be a trend for both HPZ and gastric pressure to increase by a small amount towards the end of recording and therefore it is not possible to state confidently that the duration of action of atropine on the sphincter persists for as long as 60 min. Metoclopramide has been shown to have a duration of action on the gut of 20–40 min following i.v. injection (Robinson, 1973) and our results suggest a similar duration of effect on the LOS.

It has been shown in the opossum that the action of metoclopramide on LOS is not antagonized by anticholinergic agents (Cohen and De Marino, 1976); similar findings have been reported in anaesthetized dogs (Laitinen et al., 1978). However, the results of the present study in man demonstrate that the action of metoclopramide is obscured by that of atropine when these drugs are given in clinical doses and that the effect persists for at least 40 min.

Metoclopramide acts directly on the LOS muscle at a site which is different from that of the cholinergic receptor and there is a suggestion that the drug may act as a dopamine receptor antagonist (Bauman, McCallum and Sturdevant, 1976). Dopamine is known to decrease LOS pressure in the opossum (Rattan and Goyal, 1976) and thus blockade of these receptors would theoretically lead to an increase in LOS pressure which should not be antagonized or potentiated by effects on cholinergic receptors. Although we have demonstrated in this study that atropine 0.6 mg and metoclopramide 10 mg produce changes of approximately the same magnitude, the effects of atropine appear to predominate. However, because there are many factors influencing the tone of LOS, including cholinergic, adrenergic and reflex mechanisms, it is not possible to speculate upon the mechanism of action of metoclopramide on the LOS in man.

Gastro-oesophageal reflux depends to a large extent on the barrier pressure between the stomach and the high pressure zone at the lower end of the oesophagus (Haddad, 1970; Cohen and Harris, 1971). It is therefore important for anaesthetists to consider the effects on barrier pressure of the drugs used in clinical practice. Such considerations should include not only peak effects, but also rate of onset and duration of action.

Silent regurgitation has been reported in 7.8% of a group of patients for various general surgical procedures and of those, 8.6% had evidence of pulmonary aspiration (Blitt et al., 1970). In obstetric anaesthetic practice, the frequency of maternal deaths attributed to pulmonary aspiration has remained unchanged in the last two triennial reports. It has been suggested that metoclopramide be used as a means of reducing the frequency of regurgitation (Brock-Utne et al., 1976); however, our results suggest that atropine exerts a predominant effect over metoclopramide on the LOS pressure. Any benefit of an increase in BP produced by metoclopramide would be abolished by the consecutive use of atropine.

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EFFETS INDIVIDUELS ET COMBINES DE L'ATROPINE ET DE LA METOCLOPRAMIDE SUR LA PRESSION DU SPHINCTER OESOPHAGIEN INFERIEUR

RESUME

Chez 12 volontaires en bonne santé, on a étudié les effets de l'atropine et de la metoclopramide sur la pression du sphincter oesophagien inférieur (LOSP) au moyen de transducteurs de pression oesophagienne. L'atropine a fait diminuer la LOSP de manière significative 5 min après l'injection i.v. ($P < 0{,}005$) et cette modification s'est maintenue pendant 60 min. La metoclopramide a fait augmenter la LOSP de manière significative 3 min après l'administration i.v. ($P < 0{,}05$) et cette modification s'est maintenue pendant 40 min. Après une administration consécutive de ces substances, les effets de l'atropine furent prédominants.

EINZELNE UND KOMBINIERTE EFFEKTE VON ATROPIN AUF DEN UNTEREN SPEISERÖHREN-SCHLIESSMUSKELDRUCK

ZUSAMMENFASSUNG

Die Wirkungen von Atropin und Metoclopramid auf den unteren Speiseröhren-Schliessmuskeldruck (LOSP) wurden an 12 gesunden Freiwilligen mittels Ösophageal-Druckwandlern untersucht. Atropin senkte den LOSP wesentlich—5 min nach intravenöser Verabreichung ($P < 0{,}005$), und dieser Wert blieb 60 min lang erhalten. Metoclopramid erhöhte den LOSP wesentlich—3 min nach intravenöser Verabreichung ($P < 0{,}05$), und dieser Wert blieb 40 min lang erhalten. Nach konsekutiver Verabreichung beider Drogen blieb die Wirkung von Atropin vorherrschend.

EFECTOS INDIVIDUALES Y COMBINADOS DE LA ATROPINA Y DE LA METOCLOPRAMIDA EN LA PRESION DEL ESFÍNTER ESOFÁGICO INFERIOR

SUMARIO

Se estudiaron los efectos de la atropina y de la metoclopramida en la presión del esfínter esofágico inferior (LOSP) en 12 voluntarias sanos por medio de un transductor de presión esofágica. La atropina redujo la LOSP de manera significante 5 min después de la inyección i.v. ($P < 0{,}005$) y este cambio se mantuvo durante 60 min. La metoclopramida acrecentó la LOSP de manera significante 3 min después de la administración i.v. ($P < 0{,}05$) y este cambio se mantuvo durante 40 min. Luego de la administración consecutiva de estas substancias, los efectos de la atropina predominaron.

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COMPARISON OF THE EFFECTS OF ATROPINE AND GLYCOPYRROLATE ON LOWER OESOPHAGEAL SPHINCTER PRESSURE

B. R. COTTON AND G. SMITH

SUMMARY

Lower oesophageal sphincter pressure (LOSP) has been measured on three separate occasions in nine healthy volunteers using oesophageal pressure transducers. Atropine 0.6 mg decreased LOSP significantly at 5 min after i.v. injection ($P < 0.025$) and this change was sustained for 40 min. Glycopyrrolate 0.3 mg or 0.2 mg decreased LOSP significantly at 3 min after i.v. injection ($P < 0.0025$). This change was sustained for 60 min and was similar for both doses and also similar in magnitude to the change produced by atropine.

The lower oesophageal sphincter is thought to be an important mechanism in the prevention of reflux of gastric contents into the oesophagus. The tendency to regurgitate is related to the barrier pressure (BP) which is the difference between the gastric pressure (GP) and the lower oesophageal sphincter (LOS) or high pressure zone (HPZ) pressures. It is important, therefore, for anaesthetists to be aware of the effects of their drugs, particularly premedicants, on the LOS.

It is shown in an accompanying paper that atropine decreases BP and that this change is sustained for 40 min or so (Cotton and Smith, 1981). Recently it has been suggested that glycopyrrolate, a new quaternary ammonium anticholinergic drug, may be used either for premedication (Mirakhur et al., 1978; McCubbin et al., 1979), or as an alternative to atropine in the antagonism of non-depolarizing neuromuscular blockade (Klingenmaier et al., 1972; Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977). However, it has been shown that glycopyrrolate decreases barrier pressure (Brock-Utne et al., 1978), although there was no indication of the time at which the single measurement was made following i.v. injection of the drug and no assessment of the time-course or duration of effect. Although it has been suggested that glycopyrrolate may be preferable to atropine for premedication, there has been no study comparing the effects of atropine and glycopyrrolate on LOS pressure. The purpose of this study was to compare the onset and duration of action of atropine and glycopyrrolate on BP in man.

METHODS

Informed consent to participation in this study was obtained from nine healthy volunteers (ages 21–38 yr) who had no history of gastrointestinal, respiratory or cardiovascular disease, and were not receiving any drug therapy. Five subjects were male; four were smokers. All subjects had fasted and, where relevant, refrained from smoking for at least 6 h before swallowing a silastic nasogastric tube (3 mm o.d.) into which were embedded three sub-miniature strain gauge pressure transducers at 5, 10 and 15 cm from the distal tip (Gaeltec Ltd). This was connected via a pre-amplifier to a chart recorder (Linearcorder Mk III). Each transducer was calibrated by immersion in a column of water at 37 °C.

The tube was swallowed orally until all the transducers were in the stomach and a period of 15–20 min allowed to elapse to enable gastric motility to settle.

Control measurements of gastric (GP) and high pressure zone (HPZ) pressures were made by gradual withdrawal (0.5-cm increments) of the tube from the stomach through the HPZ until all the transducers were in the oesophagus. Changes produced by swallowing were evident on the oesophageal pressure trace and recognized as previously described (Smith, Dalling and Williams, 1978) and were discarded. These techniques as used in our laboratory have been described in more

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detail in the accompanying study (Cotton and Smith, 1981).

Each volunteer swallowed the tube on three separate occasions. On the first occasion each subject received either atropine 0.6 mg i.v., glycopyrrolate 0.3 mg i.v., or glycopyrrolate 0.2 mg i.v. On the second and third occasions each received either the second or the third drug and the order of administration was randomized between subjects. Measurements were made, using the pull-through technique, at 3 min, 5 min and then 5-min intervals following the i.v. injections of the drugs until the end of recording at 60 min. At the end of recording, the tube was removed and the zero baseline and calibration re-assessed. It was found on all occasions that zero drift and changes in calibration were minimal.

All results were analysed using Student's *t* tests for paired data.

RESULTS

Atropine produced a decrease in BP from 17.5 ± 1.5 cm H_2O (mean ± SEM) to 12.9 ± 1.4 cm H_2O ($P < 0.025$) 5 min after i.v. injection. Thereafter barrier pressure remained decreased significantly until the end of recording at 60 min. However, during the final 20 min of recording there was a trend for both HPZ and gastric pressure to increase ($P < 0.05$ at 60 min) (fig. 1).

Glycopyrrolate 0.2 mg decreased BP from 23.3 ± 2.7 cm H_2O to 13 ± 1.5 cm H_2O ($P < 0.0025$) at 10 min, this reduction being both evident and significant at 3 min after injection (fig. 2). Barrier pressure remained significantly decreased until the end of recording at 60 min, as a result of a significant decrease in HPZ, whilst GP remained unchanged, in contrast to the changes seen in response to atropine.

Following glycopyrrolate 0.3 mg i.v., BP decreased from 23.2 ± 2.3 cm H_2O to 11.8 ± 1.6 cm H_2O ($P < 0.0005$) at 5 min and again this decrease was both evident and significant at 3 min after injection. Barrier pressure remained significantly decreased until the end of recording at 60 min (fig. 3).

There was no significant difference between the effects produced by glycopyrrolate 0.3 mg and those produced by a dose of 0.2 mg.

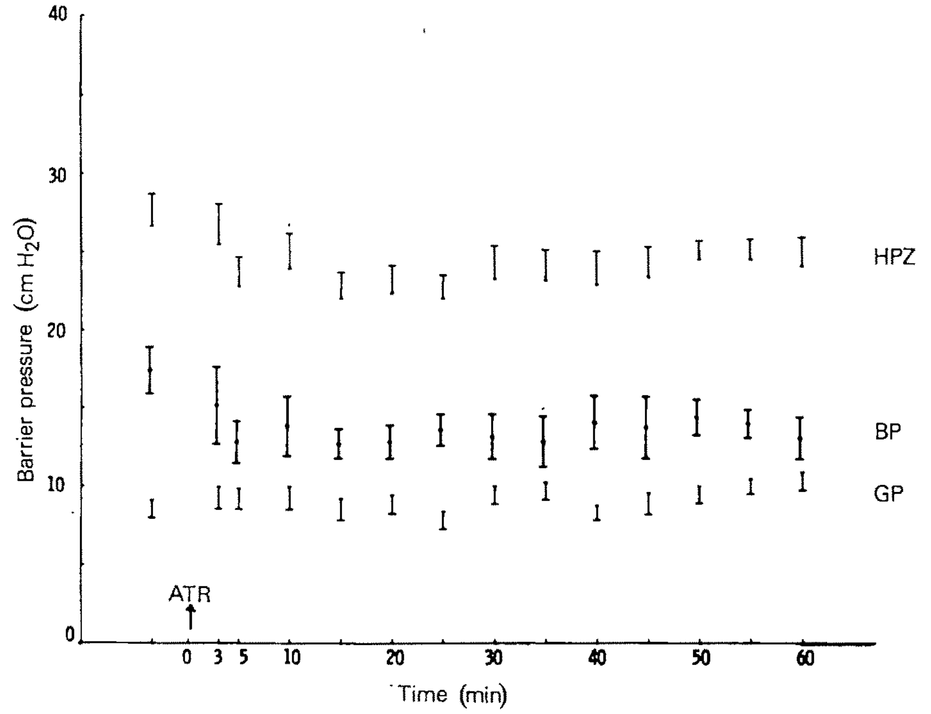

FIG. 1. Effect of atropine 0.6 mg (ATR) i.v. on high pressure zone (HPZ), barrier pressure (BP) and gastric pressure (GP) (mean values ± SEM).

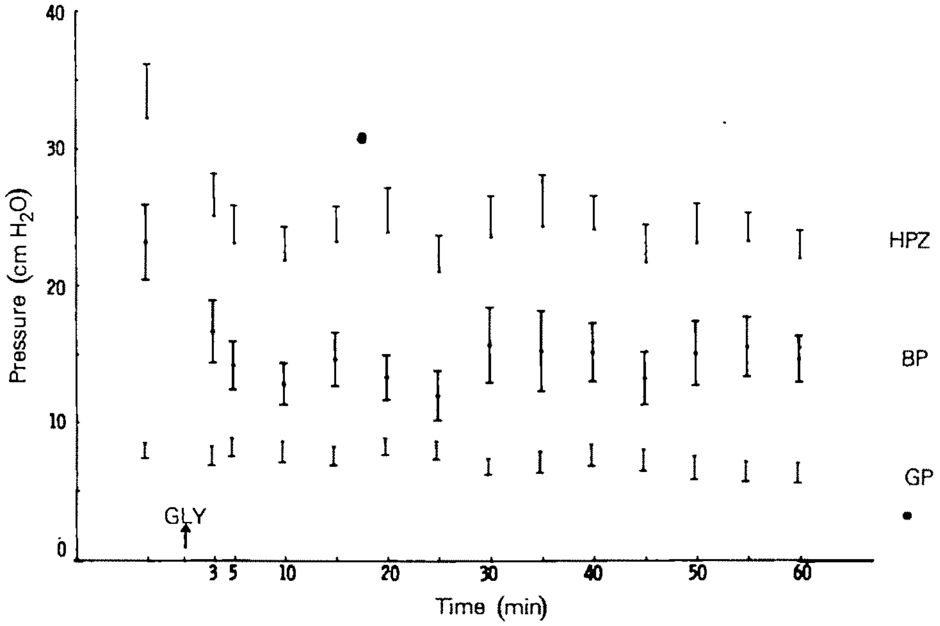

FIG. 2. Effect of glycopyrrolate 0.2 mg (GLY) i.v. on HPZ, BP and GP (mean values ± SEM).

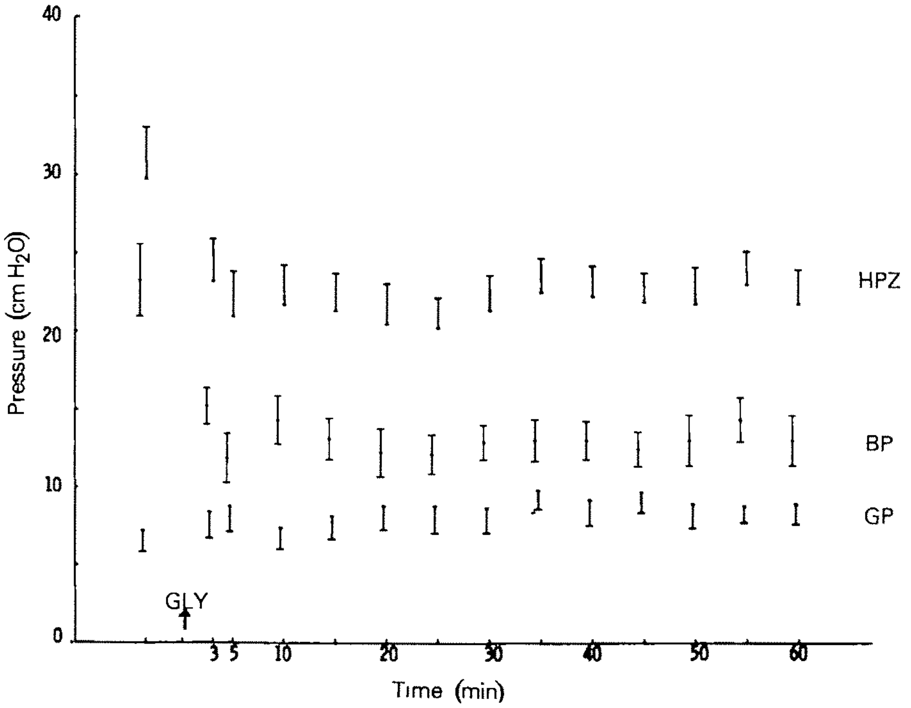

FIG. 3. Effect of glycopyrrolate 0.3 mg (GLY) i.v. on HPZ, BP and GP (mean values ± SEM).

DISCUSSION

This study confirms that glycopyrrolate 0.3 mg decreases BP (Brock-Utne et al., 1978) and showed that a dose of 0.2 mg decreased BP by the same magnitude. The decrease persisted for 60 min with both doses and the extent of decrease was of the same order as that produced by atropine 0.6 mg. Furthermore, these results suggest that the effect of glycopyrrolate on the lower oesophageal sphincter may persist for longer than the effect of atropine.

We have used two different doses of glycopyrrolate since, although 0.3 mg is quoted widely as a standard dose, we understand that the manufacturers intend to recommend for release in Great Britain an ampoule containing 0.2 mg as equivalent to an ampoule of atropine 0.6 for premedication (C. J. Jones, personal communication).

Glycopyrrolate had been shown to have longer acting and more potent antisialagogue actions than atropine (Wyant and Kao, 1974). Being a quaternary ammonium compound, the drug crosses the blood–brain barrier to a limited extent compared with atropine and should not therefore exert the central effects sometimes associated with atropine (Proakis and Harris, 1978). When used as a premedicant it produces a lower initial heart rate (McCubbin et al., 1979) and a decreased frequency of arrhythmias on induction of anaesthesia compared with atropine (Mirakhur et al., 1978). It offers protection similar to atropine against the cardiac effects resulting from intermittent administration of suxamethonium (Cozanitis, Dundee and Khan, 1980) and produces a more stable heart rate with a reduced frequency of tachycardia and arrhythmia when used in a mixture with neostigmine for antagonism of neuromuscular blockade (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clark, 1977). However, we now show that it decreases barrier pressure to an extent similar to atropine and this effect on the LOS is likely to be more prolonged. Although drugs were given by the i.v. route as opposed to the more usual s.c. or i.m. routes for premedication, it seems reasonable to assume that administration by these routes would result in changes of a lower order of magnitude. Thus, although glycopyrrolate may have advantages over atropine as a premedicant in terms of effect on heart rate (McCubbin et al., 1979) it demonstrates no advantages in terms of effects on the LOS. Anaesthetists should be alert to the fact that the administration of either anticholinergic drug may be accompanied by increased predisposition to regurgitation.

ACKNOWLEDGEMENT

We are grateful to C. J. Jones of A. H. Robins Company Limited for the supplies of glycopyrrolate.

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COMPARAISON DES EFFETS DE L'ATROPINE ET DU GLYCOPYRROLATE SUR LA PRESSION DU SPHINCTER OESOPHAGIEN INFERIEUR

RESUME

Chez neuf volontaires en bonne santé, on a mesuré à trois reprises différentes la pression du sphincter oesophagien inférieur (LOSP) au moyen de transducteurs de pression oesophagienne. L'atropine en dose de 0,6 mg a eu pour effet de faire diminuer sensiblement la LOSP 5 min après l'injection i.v. ($P < 0{,}025$) et cette modification s'est maintenue pendant 40 min. Le glycopyrrolate en dose de 0,3 mg ou 0,2 mg a fait descendre de manière significative la LOSP 3 min après l'injection i.v. ($P < 0{,}0025$). Cette modification s'est maintenue pendant 60 min et était analogue dans les deux cas et son ampleur était également analogue à celle de la modification intervenue avec l'atropine.

VERGLEICH DER WIRKUNGEN VON ATROPIN UND GLYCOPYRROLAT AUF DEN UNTEREN SPEISERÖHREN-SCHLIESSMUSKELDRUCK

ZUSAMMENFASSUNG

Der untere Speiseröhren-Schliessmuskeldruck (LOSP) wurde bei drei separaten Gelegenheiten an 9 gesunden Freiwilligen mittels Ösophageal-Druckwandlern gemessen. Atropin 0,6 mg senkte den LOSP wesentlich—5 min nach intravenöser Verabreichung ($P < 0{,}025$), was 40 min lang gehalten werden konnte. Glycopyrrolat 0,3 mg oder 0,2 mg senkte den LOSP wesentlich—3 min nach intravenöser Verabreichung ($P < 0{,}0025$), was 60 min lang gehalten werden konnte, bei beiden Dosen gleich und dem Ausmassnach auch ähnlich der Atropin-Wirkung war.

COMPARACION DE LOS EFECTOS DE LA ATROPINA Y DEL GLICOPIRROLATO SOBRE LA PRESION DEL ESFÍNTER ESOFÁGICO INFERIOR

SUMARIO

En tres oportunidades distintas, se midió la presión del esfínter esofágico inferior (LOSP) de nueve voluntarios sanos por medio de transductores de presión esofágica. Unos 0,6 mg de atropina redujeron la LOSP de manera significante 5 min después de la inyección i.v. ($P < 0{,}025$) y este cambio se mantuvo durante 40 min. El glicopirrolato en dosis de 0,3 mg ó 0,2 mg redujo la LOSP de manera significante 3 min después de la inyección i.v. ($P < 0{,}0025$). Este cambio se mantuvo durante 60 min y se asemejaba con ambas dosis así como en amplitud con el cambio provocado por la atropina.

Br. J. Anaesth. (1981), 53, 881

POSTURE AND VENTILATION DURING POSTERIOR FOSSA AND CERVICAL OPERATIONS

Current practice in the United Kingdom

T. VICTOR CAMPKIN

SUMMARY

Details of the method of lung ventilation and the preferred position of the patient during posterior fossa (infratentorial) surgery and cervical operations were sought from 37 neurosurgical centres in the United Kingdom. The sitting position remains popular (52%). Although in the majority the use of controlled ventilation is routine practice in a significant number (22%), the maintenance of spontaneous breathing is preferred, particularly during posterior fossa surgery. Although the potential hazards of the sitting position are recognized, there is no real evidence from this survey of any move to abandon its use.

The position of the patient is an important consideration during anaesthesia for neurosurgical procedures. The supine posture is almost always used during supratentorial operations, but during surgery in the posterior fossa (infratentorial) or cervical area it may be necessary to maintain anaesthesia with the patient either seated, prone or semi-prone. For approximately two decades, controlled passive hyperventilation has been almost universal during supratentorial surgery and in many institutions this technique is preferred for infratentorial operations. However, in some centres it is considered preferable to permit spontaneous breathing since this may provide some evidence of disturbance to vital centres as changes in the pattern of breathing may be observed.

To assess current practice a questionnaire was sent to all neurosurgical centres in the United Kingdom. The present paper summarizes the data received.

METHODS

A reply to the following questions was sought from a senior anaesthetist in each of 37 major neurosurgical centres in the United Kingdom. It was appreciated that in some units widely different techniques would be in routine use and in such instances details of these were requested.

(1) In what position is the patient usually placed during (a) infratentorial surgery (b) cervical surgery (excluding Cloward's operation)?

(2) Is spontaneous respiration or controlled ventilation preferred during (a) infratentorial surgery (b) cervical surgery?

(3) (a) Is the use of the prone, semi-prone or lateral position increasing?
(b) If yes, is this related to the use of controlled ventilation?

(4) What monitoring techniques are routinely used during anaesthesia in the sitting position?

RESULTS

Replies were received from 36 centres.

Infratentorial surgery (table I)

Sitting position. Nineteen centres (52.7%) prefer the sitting position and in nine of these spontaneous breathing is maintained. In one unit ventilation is controlled until the posterior fossa

TABLE I. *Position and type of ventilation during infratentorial surgery; 36 centres*

	No. of centres	(%)
Sitting position	19	52.7
Spontaneous respiration	8	
Controlled ventilation	10	
Combined technique	1	
Prone or lateral position	13	36
Spontaneous respiration	Nil	
Controlled ventilation	13	
Sitting, prone or lateral position	4	11
Spontaneous respiration	Nil	
Controlled ventilation	4	

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structures have been exposed: neuromuscular blockade is then antagonized and the patient allowed to breathe spontaneously (combined technique: table I).

Prone or semi-prone position. Either the prone or semi-prone position is used routinely in 13 centres (36%) and in these ventilation is controlled throughout.

Sitting, prone or semi-prone. In four centres (11%) all three positions are used commonly, depending on the preference of the individual surgeon or anaesthetist. However, irrespective of the position, ventilation is controlled.

Cervical surgery (table II)

The data received specifically excluded anaesthesia for Cloward's operation, since this procedure involves cervical fusion by the anterior route and is performed with the patient supine.

TABLE II. *Position and type of ventilation during cervical surgery (excluding Cloward's operation); 36 centres*

	No. of centres	(%)
Sitting position	11	30.5
Spontaneous respiration	4	
Controlled ventilation	7	
Prone or lateral position	17	47.2
Spontaneous respiration	1	
Controlled ventilation	16	
Sitting, prone or lateral position	8	22.3
Spontaneous respiration	Nil	
Controlled ventilation	8	

Sitting position. Fewer centres (30.5%) routinely use the sitting position for cervical surgery. In four, spontaneous breathing is maintained, the remainder preferring controlled ventilation.

Prone, semi-prone or lateral. These positions are used in 17 centres (47.2%): ventilation is controlled in all except one.

Sitting, prone, semi-prone or lateral. In eight centres (22.3%) both the sitting position and a recumbent position are used regularly. Controlled ventilation is always used.

Change in technique

Five centres reported that the use of a recumbent position had increased in recent years and four of these thought that this was related to the use of controlled ventilation. However, in two units the sitting position is being used more frequently. Both stated that this was principally so that junior staff could gain experience of anaesthetizing patients in this position.

Monitoring in the sitting position

Details were received from 23 centres where the sitting position is used routinely or occasionally and are presented in table III.

TABLE III. *Routine monitoring in the sitting position; 23 centres*

	No. of centres	(%)
Arterial pressure		
(a) Oscillotonometer	14	60.8
(b) Intra-arterial	20	86.9
Heart sounds	14	60.8
Electrocardiogram	23	100
Doppler probe	14	60.8
Right atrial catheter	12	52.0
End-tidal carbon dioxide	13	56.5
Respirometer	2	8.6

DISCUSSION

The sitting position is favoured during infratentorial and cervical surgery because, with the patient upright and the head well flexed, surgical access is good and the relevant anatomy visualized readily. A moderate decrease in systemic arterial pressure usually occurs and as the venous pressure at the operative site is low, there is minimal haemorrhage in the surgical field. This position permits unimpeded ventilation if spontaneous respiration is maintained and provides a better view of the face for observing responses to cranial nerve stimulation. Neurosurgical colleagues have suggested that they find it easier to operate when the patient's head is in the same spatial position as their own.

The author's usual practice is to maintain anaesthesia with the patient in the sitting position during posterior fossa and cervical operations. However, in recent years there has been a tendency to utilize the prone position more often when the proposed surgery is upon elderly patients or those in whom postural hypotension is likely. The present survey indicates that approximately half the neurosurgical centres in the United Kingdom prefer the sitting position for posterior fossa procedures. Fewer units (30%) use this position routinely for cervical operations.

Controlled hyperventilation has distinct advantages during neurosurgery. These include the ability to maintain light anaesthesia with less risk of the patient coughing or straining or developing postural hypotension when seated upright. The institution of hypocapnia leads to a decrease in cerebral blood flow and may decrease intracranial pressure. The routine use of controlled ventilation has been recommended widely (Michenfelder, Gronert and Rehder, 1969; Millar, 1972; Greenbaum, 1976; Campkin and Turner, 1980) and this technique is used in the majority of centres in the United Kingdom. However, a significant percentage of centres (22% for posterior fossa operations and 14% for cervical operations) prefer spontaneous breathing since changes in the respiratory pattern provide a warning of surgical encroachment on vital centres. Since such surgical "trespass" may also give rise to changes in arterial pressure, heart rate and cardiac rhythm, accurate monitoring is required.

In the sitting position the patient is exposed to two additional hazards—postural arterial hypotension and venous air embolism. The former implies the need for continuous and accurate recording of arterial pressure and in the majority of centres (87%) measurement of intra-arterial pressure is used routinely. A variety of techniques is available for the early detection of venous air embolism, including the Doppler ultrasonic probe, measurement of end-tidal carbon dioxide concentration and, most recently, measurement of pulmonary artery pressure (PAP) using a flow-directed catheter (Maroon, Edmonds-Seal and Campbell, 1969; Brechner and Bethune, 1971; Munson et al., 1975). The insertion of a right atrial catheter is common practice and enables the anaesthetist to confirm the entry of air into the heart and, on occasions, to aspirate significant quantities of air. These devices may be used in varying combinations and the author's practice is to combine the insertion of a right atrial catheter with a Doppler probe and measurement of intra-arterial pressure. PAP monitoring does not appear to be in use in any centre in this country.

The present survey indicates that, in the United Kingdom, the sitting position is used widely during neurosurgery despite the attendant dangers and there is little evidence of any recent change in favour of the recumbent position. The same would appear to be the case in North America and the literature suggests that attention has been directed more to the early detection of air embolism than to any widespread abandoning of this posture. In several centres (22%) the maintenance of spontaneous respiration is preferred, particularly during infratentorial operations. However, in common with other writers, the author's view is that the benefits of controlled hyperventilation outweigh the single advantage derived from maintaining spontaneous breathing. It is believed that accurate monitoring of the heart rate, systemic arterial pressure and e.c.g. provides reliable evidence of disturbance to the vital centres (Michenfelder, Gronert and Rehder, 1969; Shapiro, 1975; Greenbaum, 1976).

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POSTURE ET VENTILATION PENDANT LES OPERATIONS A LA FOSSE POSTERIEURE ET AU CERVEAU

Pratique courante au Royaume-Uni

RESUME

On a interrogé 37 centres de neurochirurgie du Royaume-Uni pour avoir des détails sur la méthode de ventilation utilisée et sur la position qu'ils préfèrent donner aux patients lors des interventions chirurgicales sur la fosse postérieure (infratentorielle) et lors des opérations au cerveau. La position assise demeure la position la plus courante (52%). Bien que dans la majorité des cas, la pratique courante de l'usage de la ventilation contrôlée soit importante (22%), on préfère maintenir la respiration spontanée, surtout pour les interventions chirurgicales sur la fosse postérieure, et bien que l'on reconnaisse que la position assise présente certains dangers, rien ne semble laisser penser, d'après notre enquête, que l'on envisage d'abandonner cette pratique.

Br. J. Anaesth (1981), 53, 885

VERAPAMIL AS A HYPOTENSIVE AGENT DURING NEUROLEPTANAESTHESIA

M. ZIMPFER, S. FITZAL AND L. TONCZAR

SUMMARY

The haemodynamic effects of verapamil were investigated in 11 patients anaesthetized with thiopentone, fentanyl and dehydrobenzperidol. Suxamethonium and pancuronium bromide were used for muscle relaxation. Verapamil 0.07 mg kg^{-1} given as a single intravenous bolus decreased mean arterial pressure from 108±18 mm Hg to 84±20 mm Hg ($P<0.001$) and total peripheral resistance by 29±10% from 1662±399 dyne s cm^{-5} ($P<0.001$) while heart rate and mean pulmonary artery pressure showed only minor changes. The decrease in arterial pressure was caused by reduction in total peripheral resistance while cardiac output was increased.

While the beneficial effects of calcium antagonists for the treatment of ischaemic heart disease (Krikler, 1974; Andreasen et al., 1975; Singh, 1975), re-entrant atrial tachyarrhythmia, controlling ventricular rate in atrial flutter and fibrillation have been documented extensively (Schamroth, Krikler and Garrett, 1972; Krikler and Spurell, 1974; Spurell, Krikler and Sowton, 1974), there are few data on the haemodynamic effects of verapamil administered i.v. in conscious and anaesthetized man. Moreover, although verapamil has been shown to be of value in the initial treatment of severe hypertensive crisis and to be safe in the presence of renal insufficiency, data on its hypotensive effects remain inconclusive (Singh, Ellrodt and Peter, 1978). The aim of this investigation was to evaluate the haemodynamic effects of an i.v. bolus injection of verapamil in man, and to determine if the therapeutic principle of specific calcium antagonism can be used in anaesthetized patients to reduce impedance to ventricular ejection during surgical procedures.

METHODS

Eleven patients, aged 54–65 yr, undergoing abdominal surgery were studied. Each was informed about the nature of the proposed investigation, and informed consent as well as institutional approval were obtained. Five patients had a history of mild hypertension, but those with clinically detectable cardiac respiratory or liver disease or who had received digoxin or beta blockers were excluded from the investigation.

A 20-gauge Tygon catheter was inserted percutaneously to the radial artery under local anaesthesia and a thermodilution Swan–Ganz catheter was placed in the pulmonary artery via a basilic vein or the right internal jugular vein. Arterial and pulmonary artery pressures were measured electromanometrically (Bentley transducers) and serial determinations of cardiac output were made using the thermodilution technique (Kimray Medical Assoc. mod. 3500). Derived measurements included ventricular stroke volume and total peripheral vascular resistance.

The patients were premedicated with diazepam 0.15 mg kg^{-1} i.m. and anaesthetized with thiopentone 180–300 mg i.v., fentanyl 0.15–0.30 mg i.v. and dehydrobenzperidol 2.5–7.5 mg i.v. after cholinergic blockade with atropine 0.3–0.5 mg i.v. Ventilation of the lungs was controlled with oxygen and nitrous oxide (FI_{O_2} 0.3) and adjusted to give a tidal volume of 10–12 ml kg^{-1} at a rate of 8–10 litre min^{-1}. Suxamethonium 60–80 mg i.v. and pancuronium bromide 4–6 mg i.v. were used for muscle relaxation. Ringer's solution 0.5–1 litre was infused throughout the study. When a steady haemodynamic baseline had been achieved after induction of anaesthesia, verapamil (Isoptin) 0.07 mg kg^{-1} was given as a single bolus i.v. In two patients calcium gluconate 15 mg kg^{-1} was given i.v. after 1–2 min. Serial measurements of cardiac output were made under control conditions and at 1, 2, 3, 5, 10 and 20 min after giving verapamil.

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The data are expressed as means ± SD. Group means for each determination were compared using Student's *t* test for paired data. *P*-values of less than 0.05 were accepted as significant.

RESULTS

Verapamil 0.07 mg kg^{-1} given as a single bolus i.v. during neuroleptanaesthesia and controlled ventilation, elicited an immediate haemodynamic response with maximum changes about 1 min after administration. After 20 min the variables measured had returned to control values, except for mean arterial pressure which was still slightly but significantly less than control. While the time course of the haemodynamic response is shown in figures 1 and 2, only the maximum changes are presented here. Mean arterial pressure decreased from 108 ± 18 mm Hg to 84 ± 20 mm Hg ($P < 0.001$) and total peripheral resistance from 1662 ± 399 to 1197 ± 390 dyne s cm^{-5} ($P < 0.001$). However, the absolute values of heart rate and mean pulmonary artery pressure were not changed significantly. At the time of maximum arterial pressure decrease, ventricular stroke volume increased from 67 ± 10 to 72 ± 13 ml ($P < 0.05$). While the QRS and Q–T intervals of the electrocardiogram were unaffected, and the R–R interval was decreased only initially (by 19.2 ± 24.2 ms; $P < 0.05$), the P–R interval remained increased throughout the study (by 21.7 ± 4.1 ms; $P < 0.001$) (table I). In two patients the cardiovascular effects of verapamil were abolished by giving calcium gluconate 15 mg kg^{-1} i.v. No significant side-effects were associated with the injection of verapamil; in particular there was no e.c.g. evidence of ischaemia.

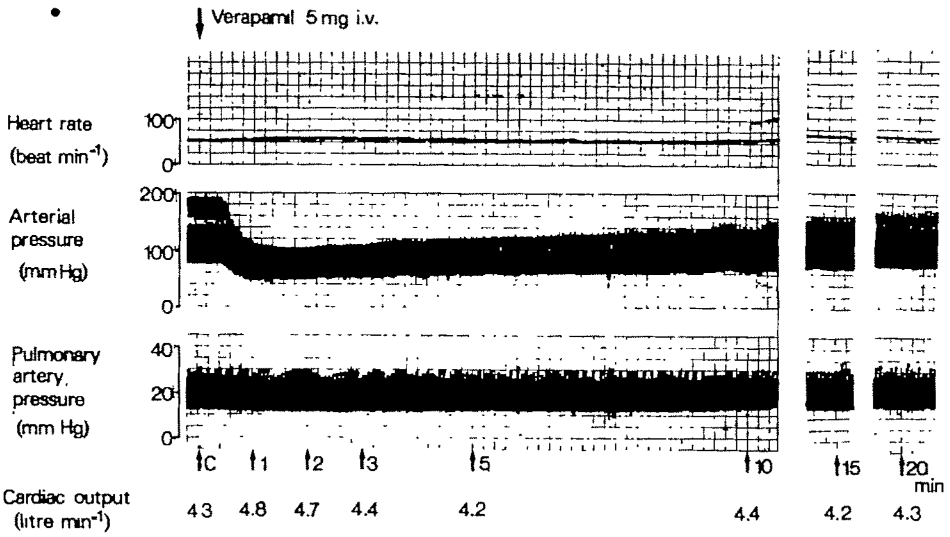

FIG. 1. Recordings of heart rate, systemic and pulmonary artery pressures are shown, with cardiac output values under control conditions and 1, 2, 3, 5, 10, 15 and 20 min after verapamil. The decrease in arterial pressure was not associated with an increase in heart rate.

DISCUSSION

This study indicates that verapamil 0.07 mg kg^{-1} given as a bolus i.v. produces a rapid but controlled and predictable reduction in mean arterial pressure. Even at the peak reduction of arterial pressure, neither a significant increase in heart rate nor a reduction in cardiac output occurred despite the well known negative inotropic action of calcium antagonists (Fleckenstein, 1970). While the QRS and Q–T intervals remained unchanged and the R–R interval increased only initially, verapamil produced a significant increase in P–R interval which reflects a prolongation in atrioventricular conduction time. The haemodynamic effects of verapamil were abolished by calcium gluconate 15 mg kg^{-1} i.v.

Verapamil is a synthetic derivative of papaverine and was first introduced as a smooth muscle relaxant with potent peripheral and coronary vasodilator properties in animals as well as in man (Singh, Ellrodt and Peter, 1978). Subsequently, electrophysiological studies in different tissues revealed that verapamil has a unique cellular

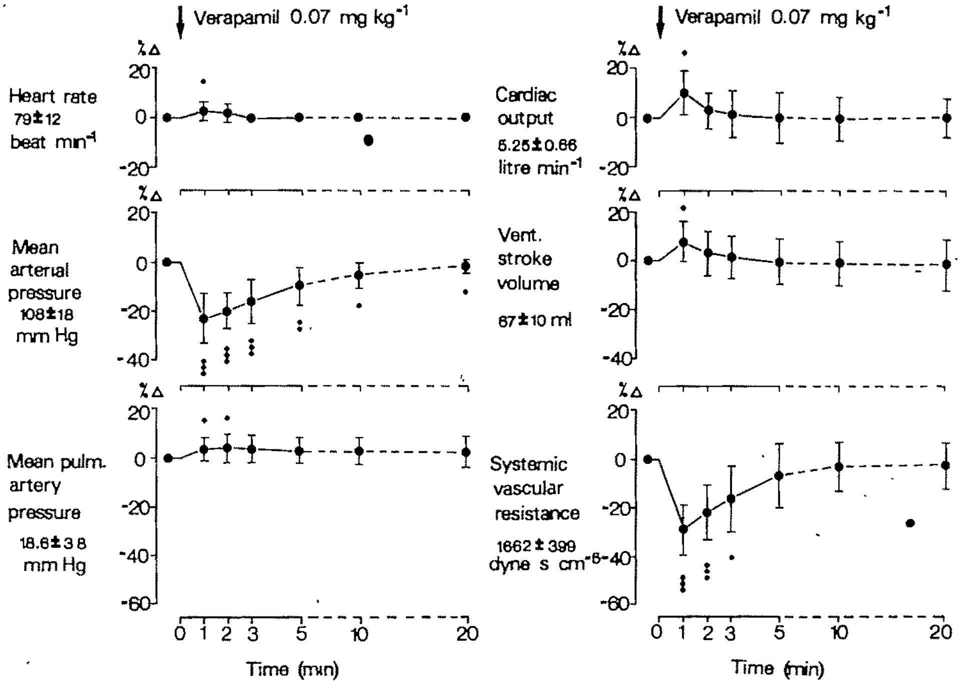

FIG. 2. Mean ± SD changes from control after a bolus injection of verapamil are shown for heart rate, mean arterial pressure, cardiac output, ventricular stroke volume and systemic vascular resistance. The negative inotropic action of the drug is opposed by its effects on afterload ($n = 9$).

TABLE I. *Electrocardiographic features before and after verapamil 0.07 mg kg^{-1}. *$P < 0.05$; ***$P < 0.001$*

Interval (ms)	Before verapamil	After verapamil					
		1 min	2 min	3 min	5 min	10 min	20 min
R–R	769±86	749±90*	758±84	769±86	769±86	769±86	769±86
P–R	180±18	197±18***	201±12***	201±13***	202±16***	197±23***	200±18***
QRS	58.7±15.1	61.0±14.8	61.3±15.1	62.8±14.2	64.3±13.7	62.0±14.2	62.0±14.2
Q–T	377±50	380±51	383±46	385±45	380±51	379±50	382±52

action in selectively inhibiting the transmembrane flux of calcium (Fleckenstein et al., 1969; Kolhardt et al., 1972). As calcium ions act as a mediator between the biochemical events at the cell surface and the intercellular biochemical processes which utilize ATP for contraction (Hasselbach and Weber, 1965; Ebashi and Endo, 1968; Katz, 1970), the specific interference with calcium transport is thought to account for its antiarrhythmic and negative inotropic effects (Fleckenstein, 1970). Thus, the fundamental action of verapamil on the heart muscle is distinct from that of beta adrenergic blockers since its main site of action is the superficially located membrane storage sites for calcium (Naylor and Krikler, 1974). Specific calcium antagonism at the vascular smooth muscle cells leads to peripheral and coronary vasodilatation (Grün and Fleckenstein, 1972; Golenhofen and Hermstein, 1975).

It has been shown experimentally that verapamil does not affect the velocity of depolarization of atrial, Purkinje and ventricular fibres (Singh and Vaughan-Williams, 1972; Cranefield, Aronson and Wit, 1974). Similarly, the drug has no depressant effect on the intra-atrial, His–Purkinje and intraventricular conduction times (Neuss and Schlepper, 1971; Husaini et al., 1973; Landmark and Amlie, 1976). However, calcium ions cause the slow initial inward current in excitable tissues with pacemaker characteristics and are responsible for sinus rhythmicity and delayed atrioventricular conduction (Zipes and Fischer, 1974; Okada, 1976). Verapamil therefore produces a reduction of conduction velocity within the atrioventricular node and an increase in the refractory period of the atrioventricular node. The drug produces a complex interaction of alterations in pre-load, afterload, myocardial contractility and cardiac pacemaker function. Since ventricular stroke volume was not reduced after administration, the negative inotropic action of verapamil seems to be substantially minimized by its effects on afterload. On the other hand, the minimal effects on heart rate could be explained by the fact that reflex tachycardia, which may be expected following hypotension, is largely prevented by the drug's depressant action on the sinoatrial node. In contrast, hypotension with sodium nitroprusside is often associated with an increase in heart rate and a decrease in cardiac output (Zimpfer, Fitzal and Semsroth, 1980). This combination of chronotropic stimulation and arterial hypotension has been found to depress contractility of ischaemic myocardium (Vatner and Baig, 1979).

Verapamil is considered to be of value in the treatment of ischaemic heart disease (Krikler, 1974; Andreasen et al., 1975; Singh, 1975) since it decreases myocardial oxygen requirement (Fleckenstein, 1970) and dilates extramural coronary arteries (Grün and Fleckenstein, 1971). Chiariello and others (1976) showed that sodium nitroprusside may cause intracoronary steal and it has been found, in anaesthetized dogs, that, by preferentially dilating coronary arterioles, sodium nitroprusside could predispose to changes leading to coronary steal (Capurro, Kent and Epstein, 1977). Furthermore, in contrast to sodium nitroprusside, verapamil does not possess any known toxicity.

In conclusion, the specific calcium antagonism of verapamil can be used to reduce impedance to left ventricular ejection during neurolept anaesthesia. However, care should be taken in patients with little cardiovascular reserve. In addition, as the depressant effects of verapamil, beta adrenergic blockers and digitalis glycosides are likely to be additive, verapamil may enhance the degree of A–V block if administered in combination with these drugs.

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VERAPAMIL UTILISE EN TANT QU'AGENT HYPOTENSIF PENDANT LES ANESTHESIES NEUROLEPTIQUES

RESUME

Nous avons fait des recherches sur les effets hémodynamiques du Vérapamil sur 11 patients anesthésiés à l'aide de thiopentone, de fentanyl et de déshydrobenzpéridol. Le suxaméthonium et le bromure de pancuronium ont été utilisés pour la relaxation musculaire. Le vérapamil administré en un seul bol intraveineux de 0,07 $mg\,kg^{-1}$ a fait tomber la pression artérielle moyenne de 108 ± 18 mm Hg à 84 ± 20 mm Hg ($P < 0{,}001$) et la résistance périphérique totale de $29 \pm 10\%$, lorsque celle-ci était de 1662 ± 399 $dyne\,s\,cm^{-5}$ ($P < 0{,}001$), alors que la fréquence cardiaque et la pression artérielle pulmonaire moyenne n'ont accusé que de faibles variations. La baisse de la pression artérielle a été causée par une réduction de la résistance périphérique totale alors que le débit cardiaque augmentait.

VERAPAMIL ALS HYPOTONISCHES MITTEL BEI NEUROLEPTISCHER NARKOSE

ZUSAMMENFASSUNG

Die hämodynamischen Wirkungen von Verapamil wurde an 11 Patienten untersucht, die mit Thiopenton, Fentanyl und Dehydrobenzperidol narkotisiert waren. Suxamethonium und Pancuroniumbromid wurden zur Muskelentspannung benutzt. Verapamil 0,07 $mg\,kg^{-1}$, als einzelne intravenöse Bolus-Injektion verabreicht, senkte den mittleren arteriellen Druck von 108 ± 18 mm Hg auf 84 ± 20 mm Hg ($P < 0{,}001$), und den gesamten peripheren Widerstand um $29 \pm 10\%$ von 1662 ± 399 $Dyn\,s\,cm^{-5}$ ($P < 0{,}001$), während Herztätigkeit und mittlerer Pulmonararteriendruck nur geringfügige Veränderungen zeigten. Der arterielle Druckabstieg wurde durch die Verringerung des gesamten peripheren Widerstandes bewirkt, während sich das Herzminutenvolumen erhöhte.

VERAPAMIL COMO UN AGENTE HIPOTENSIVO DURANTE LA ANESTESIA NEURAL

SUMARIO

Se investigaron los efectos hemodinámicos del verapamil en 11 pacientes anestesiados con tiopentona, fentanilo y deshidrobenzoperidol. Se usó suxametonio y bromuro de pancuronio para la relajación muscular. La administración de verapamil, 0,07 $mg\,kg^{-1}$, cual bolo intravenoso único, disminuyó la presión arterial media desde 108 ± 18 mm Hg hasta 84 ± 20 mm Hg ($P < 0{,}001$) y la resistencia periférica total en $29 \pm 10\%$, desde $1{,}662 \pm 399$ $dyn\,s\,cm^{-5}$ ($P < 0{,}001$), al tiempo que el ritmo cardiaco y la presión arterial media pulmonar mostró tan sólo pequeños cambios. La disminución de la presión arterial la produjo una reducción de la resistencia periférica total al tiempo que la producción cardiaca incrementó.

Br. J. Anaesth. (1981), 53, 891

COMPARISON OF NITROPRUSSIDE AND NITROGLYCERINE FOR CONTROLLING HYPERTENSION DURING CORONARY ARTERY SURGERY

M. A. TOBIAS

SUMMARY

The haemodynamic effects of infusing sodium nitroprusside or trinitroglycerine to control hypertension during operation were compared in 22 patients undergoing coronary artery surgery. Measurements were taken before induction of anaesthesia, during median sternotomy, and upon attainment of a stable decrease in arterial pressure. Both drugs significantly decreased arterial pressure without affecting heart rate or cardiac output. Systemic vascular resistance, pulmonary capillary wedge pressure and left and right ventricular stroke work were decreased also. Although nitroglycerine significantly decreased pulmonary vascular resistance, and produced a significantly greater decrease in central venous pressure than nitroprusside, these differences are unlikely to be important clinically.

Systemic hypertension, sometimes accompanied by electrocardiographic evidence of ischaemia, is common before cardiopulmonary bypass in patients with coronary artery disease during revascularization operations, despite apparently adequate anaesthesia (Arens et al., 1972). Sympathetic nerve stimulation during median sternotomy may cause tachycardia and an increase in systemic vascular resistance, thus increasing ventricular stroke work and myocardial oxygen demands beyond available supply, and the patient is exposed to the danger of the perioperative infarct (Mundth and Austen, 1975).

Sodium nitroprusside (Lappas et al., 1976) and trinitroglycerine (Kaplan and Jones, 1979) have been advocated to control hypertension during cardiac surgery and this study was designed to compare these two drugs.

PATIENTS AND METHODS

Consecutive patients presenting for coronary artery bypass surgery were divided randomly into two equal groups to receive either sodium nitroprusside (SNP) or trinitroglycerine (TNG) during anaesthesia. Informed consent was obtained from each patient.

Patients

Eleven patients received SNP (nine male and two female) with a mean age of 53 yr (range 45–65 yr) and mean left ventricular end-diastolic pressure (LVEDP) on cardiac catheterization of 17 mm Hg (range 10–30 mm Hg). Eleven male patients received TNG (mean age was 51 yr, range 39–62 yr) with a mean LVEDP of 17 mm Hg (range 12–26 mm Hg). All patients had presented with angina and were treated with adrenergic beta-receptor blocking agents up to the evening before surgery. They were exercised before operation to the point of development of angina pectoris or S-T segment change on the electrocardiogram (e.c.g.), using a standard treadmill test, and rate–pressure products were calculated (Nelson et al., 1974).

Following premedication with lorazepam 2.5 mg orally (2 h before operation), and droperidol 5–10 mg plus fentanyl 50–100 μg i.m. (1 h before operation) each patient was brought to the operating theatre breathing oxygen. Cannulae were inserted, under local anaesthesia, to a peripheral vein and the radial artery. The e.c.g. (leads II and V5) was monitored and a triple-lumen thermodilution flotation catheter inserted into a branch of the pulmonary artery. The following baseline values were recorded before induction of anaesthesia: heart rate, systolic arterial pressure, mean arterial pressure, mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, mean central venous pressure and cardiac output in duplicate by thermodilution (values accepted if within 5% of each other).

Anaesthesia, induced with droperidol $0.2\,mg\,kg^{-1}$ plus fentanyl $10\,\mu g\,kg^{-1}$ i.v. was maintained with a mixture of 50% oxygen and

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nitrous oxide delivered from a Blease ventilator. The trachea was intubated following the administration of pancuronium 0.1 mg kg^{-1}. Further increments of fentanyl and pancuronium were administered as necessary (judged clinically and by interpretation of a Cerebral Function Monitor recording). Ventilation was adjusted to produce Pa_{CO_2} between 4.5 and 5.5 kPa, as determined by repeated measurements of blood-gas tensions. Before median sternotomy a 14-gauge central venous catheter was inserted percutaneously into the left subclavian vein by the infraclavicular route to allow administration of SNP or TNG.

During surgical stimulation, the patients were allowed to exceed 75% of their calculated rate–pressure product and all variables measured again (control). Either fresh 0.01% sodium nitroprusside (Nipride, Roche) in 5% dextrose (protected from light) or 0.01% trinitroglycerine (Tridil, American Hospital Supply) in 5% dextrose was infused using an electronic finger-pump counter and micro-drip set, starting at 20 µg min^{-1} and increasing by 20-µg increments each minute until mean arterial pressure decreased to between 70 and 80 mm Hg, and all measurements repeated (treatment). The time taken from commencement of infusion to attainment of a stable arterial pressure was noted. Blood losses were minimal during the study and were replaced on a 1 : 1 basis using 5% dextrose solution.

Additional variables were derived from the basic measurements as follows:

$$\mathrm{CI} = \mathrm{CO}/\mathrm{BSA}$$

$$\mathrm{SI} = \mathrm{CI}/\mathrm{HR}$$

$$\mathrm{SVRI} = (\overline{\mathrm{AP}} - \overline{\mathrm{RAP}})/\mathrm{CI}$$

$$\mathrm{PVRI} = (\overline{\mathrm{PAP}} - \overline{\mathrm{PCWP}})/\mathrm{CI}$$

$$\mathrm{LVSWI} = \frac{1.36\,(\overline{\mathrm{AP}} - \overline{\mathrm{PCWP}})}{100} \times \mathrm{SI}$$

$$\mathrm{RVSWI} = \frac{1.36(\overline{\mathrm{PAP}} - \overline{\mathrm{RAP}})}{100} \times \mathrm{SI}$$

$$\mathrm{RPP} = \mathrm{HR} \times \mathrm{SAP}$$

where CI = cardiac index (litre min^{-1} m^{-2}); SI = stroke index (ml beat^{-1} m^{-2}); SVRI = systemic vascular resistance index (mm Hg litre^{-1} min m^{2}); PVRI = pulmonary vascular resistance index (mm Hg litre^{-1} min m^{2}); LVSWI = left ventricular stroke work index (g m m^{-2}); RVSWI = right ventricular stroke work index (g m m^{-2}); RPP = rate–pressure product (mm Hg beat min^{-1}); CO = cardiac output (litre min^{-1}); BSA = body surface area (m^{2}); HR = heart rate (beat min^{-1}); $\overline{\mathrm{AP}}$ = mean arterial pressure (mm Hg); $\overline{\mathrm{RAP}}$ = mean right atrial pressure (mm Hg); $\overline{\mathrm{PAP}}$ = mean pulmonary artery pressure (mm Hg); $\overline{\mathrm{PCWP}}$ = mean pulmonary capillary wedge pressure (mm Hg) and SAP = systolic arterial pressure (mm Hg).

Results are expressed as mean ± standard error of the mean (SEM), and paired and unpaired Student *t* tests used for assessment of statistical significance.

RESULTS

The haemodynamic changes produced by SNP or TNG are presented in table I.

During opening of the chest and before preparation of the heart for cardiopulmonary bypass, surgical stimulation produced an increase in heart rate in both groups of patients (fig. 1). However, there was no further increase after the introduction of either SNP or TNG.

Median sternotomy was associated with marked systemic hypertension which was not ameliorated by increments of fentanyl 200 µg i.v. Within 1 min of commencing an infusion of SNP there was a decrease in mean arterial pressure and stability was achieved within 5 min at an average dose of 1.1 µg kg^{-1} min^{-1}. There was a marked tendency to overshoot, but arterial pressures returned to baseline values within 4 min of stopping the infusion.

TNG produced a significant decrease in arterial pressure (fig. 2) which was more gradual in onset. The effects were seen within 2 min of commencing the infusion and stability was achieved within 7 min at an average dose of 2.8 µg kg^{-1} min^{-1}. There was less tendency to overshoot than with SNP. Arterial pressures returned to their previous values within 5 min of withdrawing TNG.

The changes in mean arterial pressure were reflected in significant decreases in RPP (table II). Although two patients receiving SNP developed transient S-T segment depression during surgical stimulation, this reverted to normal during the infusion of SNP. S-T segments remained iso-electric throughout in the TNG group.

Left atrial pressures decreased markedly during administration of SNP or TNP and the latter agent

TABLE I. *Haemodynamic effects of sodium nitroprusside (SNP) or trinitroglycerine (TNG) in patients during coronary artery surgery. Mean ± SEM. Symbols for statistical significance (Student's t tests): *$P < 0.05$; **$P < 0.005$. Difference in change of central venous pressure from control value produced by SNP compared with that produced by TNG was the only change statistically significant between SNP and TNG*

	SNP group ($n = 11$)		TNG group ($n = 11$)	
	Control	SNP	Control	TNG
Heart rate (beat min^{-1})	88±6	89±5	80±5	83±5
Mean arterial pressure (mm Hg)	120±7	75±2**	115±6	81±2**
Mean pulmonary arterial pressure (mm Hg)	20±2	12±2**	18±2	9±1**
Pulmonary capillary wedge pressure (mm Hg)	15±2	6±1**	13±2	5±1**
Central venous pressure (mm Hg)	4±1	3±1*	5±1	2±1**
Cardiac index (litre min^{-1} m^{-2})	2.05±0.15	2.04±0.15	2.21±0.15	2.16±0.09
Stroke index (ml $beat^{-1}$ m^{-2})	23.8±1.9	23.4±1.8	28.4±2.2	26.9±1.8
Systemic vascular resistance index (mm Hg $litre^{-1}$ min m^2)	60±5.7	37.3±3**	52.3±5.2	36.8±2.1*
Pulmonary vascular resistance index (mm Hg $litre^{-1}$ min m^2)	2.69±0.48	2.56±0.39	2.60±0.25	2.16±0.20*
Left ventricular stroke work index (g m m^{-2})	32.9±2.7	21.5±1.6**	39.1±3.9	27.8±1.9*
Right ventricular stroke work index (g m m^{-2})	4.8±0.61	2.76±0.31**	4.83±0.52	2.90±0.26**
Rate–pressure product (mm Hg beat min^{-1})	14571±1669	9114±742**	12521±956	9318±686**

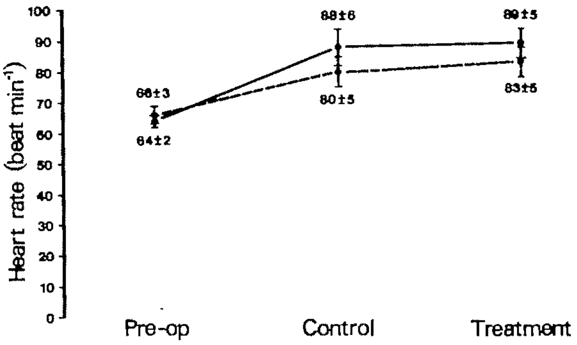

FIG. 1. Changes in heart rate from pre-induction values (pre-op), during surgical stimulation (control), and after vasodilator therapy (treatment). Values are expressed as mean ± SEM. Changes from control for both drugs were not significant; differences between drugs not significant. —— = Nitroglycerine group, --- = nitroprusside group.

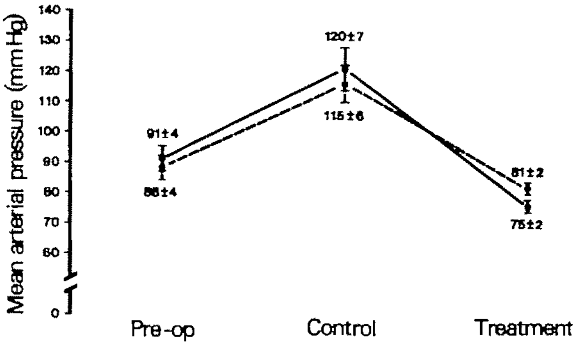

FIG. 2. Changes in mean arterial pressure in patients receiving either nitroglycerine (——) or nitroprusside (----) compared with values during surgery (control) or before induction of anaesthesia (pre-op). Changes in both groups were significant ($P < 0.01$); differences between groups not significant.

produced a slightly greater decrease in right atrial pressure than that achieved by SNP.

Cardiac index and stroke index decreased in both groups after the induction of anaesthesia (fig. 3) despite an increase in mean arterial pressure with surgical stimulation. These indices were unaffected by the infusion of SNP or TNG.

Systemic vascular resistance index decreased markedly in both groups during treatment. Although the decrease was greater in the patients receiving SNP the difference was not statistically significant. Pulmonary vascular resistance was unaffected by SNP but decreased significantly with TNG although the difference between the groups was not significant.

Left ventricular performance was improved markedly by both drugs (figs. 4, 5). Two patients in the SNP group and five in the TNG group who

TABLE II. *Rate–pressure product* (*mm Hg beat min*$^{-1}$). *Differences between SNP and TNG not significant*

	Sodium nitroprusside	Trinitroglycerine
Angina threshold on exercise treadmill	17755	16053
Maximum RPP during sternotomy	14571 ±1669	12521 ±956
RPP after stability achieved with vasodilators	9114 ±742 $P<0.001$	9318 ±686 $P<0.001$

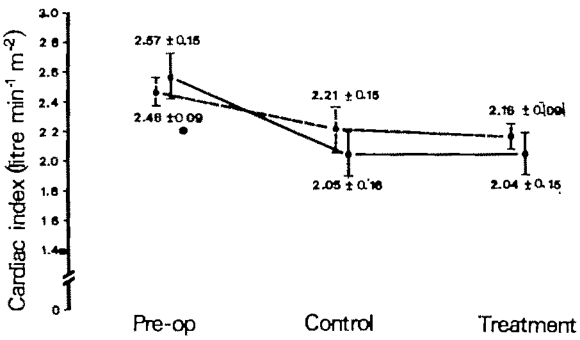

FIG. 3. Effects of nitroprusside (——) or nitroglycerine (- - -) on cardiac index (CI). Changes within groups and difference between groups not significant.

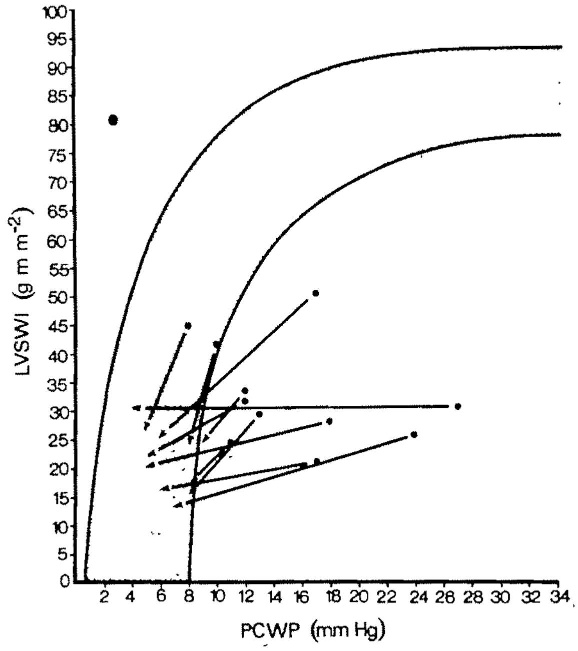

FIG. 4. Left ventricular stroke work index (LVSWI) plotted against pulmonary capillary wedge pressure (PCWP). Hatched area represents normal left ventricular function curve. Dots represent values obtained from 11 patients during surgical stimulation. Arrow-heads joined by solid lines show changes produced by nitroprusside infusion.

possessed normal left atrial pressures and stroke work indices during surgical stimulation responded normally to vasodilatation by concomitant decreases in both parameters. Nine patients treated with SNP, and six patients treated with TNG, who had abnormally high left atrial pressures during surgical stimulation, responded to vasodilatation by a decrease in left atrial pressure to normal without any corresponding decrease in ventricular stroke work.

DISCUSSION

Sympathetic nerve stimulation increases myocardial oxygen consumption by increasing heart rate, augmenting contractility, and increasing intramyocardial wall tension secondary to increased afterload (hypertension) or increased preload (increased ventricular filling pressures) (Braunwald, 1971).

Measurement of the rate–pressure product as a guide to myocardial oxygen consumption ($\dot{V}m_{O_2}$) during anaesthesia is controversial and has its advocates (Dunbar, 1979) and detractors (Kissin and Mardis, 1980). Since the components of the RPP produce opposite effects on myocardial oxygenation, changes in RPP may not accurately reflect changes in $\dot{V}m_{O_2}$ (Barash and Kopriva, 1980). An increase in heart rate increases $\dot{V}m_{O_2}$ and decreases the time available for coronary filling during diastole. An increase in systolic arterial pressure may increase $\dot{V}m_{O_2}$ but may also improve myocardial oxygenation by increasing coronary perfusion pressure. Thus, a patient with tachycardia and hypotension may be in greater danger of suffering ischaemic cardiac damage than one with a numerically similar RPP produced by systolic hypertension and a normal heart rate. In this study, increases in heart rate and systolic arterial pressure were evenly matched in both groups, hence RPP measurement could be expected to provide a reasonable clinical guide to an increase in $\dot{V}m_{O_2}$ and the possibility of ischaemia, whilst accepting the limitations of this index as outlined above.

One approach to the control of hypertension and tachycardia during anaesthesia for coronary artery

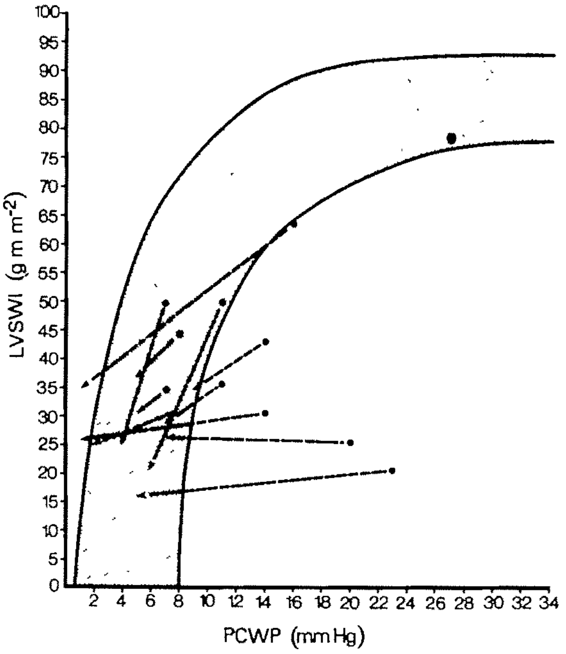

FIG. 5. Left ventricular stroke index (LVSWI) plotted against pulmonary capillary wedge pressure (PCWP). Hatched area represents normal left ventricular function curve. Dots represent values obtained from 11 patients during surgical stimulation. Arrow-heads joined by dotted lines show changes produced by nitroglycerine infusion.

surgery is to utilize maximal beta-blockade by continuing treatment right up to the morning of surgery. However, such therapy may impair the normal inotropic response of the heart to the moderate haemodilution which occurs after cardiopulmonary bypass, and so produce a situation where the cardiac output cannot increase sufficiently to guarantee adequate oxygen transport to the tissues (Clarke et al., 1980). An alternative is to increase the depth of anaesthesia by the administration of inhalation agents. However, halothane, enflurane and trichloroethylene cause depression of ventricular function, especially in the presence of beta-adrenergic blocking agents (Stephen, Davie and Scott, 1971; Foëx et al., 1974 Horan et al., 1977), and are associated with high ventricular filling pressures and poor endocardial viability ratios (Maunuksela, 1977; van Ackern et al., 1979).

Investigations in dogs using epicardial mapping (Bland and Lowenstein, 1976), and direct measurement (Smith, Rogers and Thorburn, 1980) have demonstrated that halothane improves the ratio of oxygen supply to demand in experimentally-produced myocardial ischaemia in the presence of normal ventricular filling pressures. This beneficial effect has yet to be demonstrated in the presence of increased ventricular filling pressures in man. It would therefore seem logical to control hypertension during operation by the adoption of an anaesthetic technique which has a reputation for maintaining cardiovascular stability without depressing ventricular function (Tydén and Westerholm, 1979) by using moderate beta-blockade (by discontinuing beta-blocking agents 12–24 h before surgery) and augmenting these with direct-acting vasodilators.

Kaplan and Jones (1979) compared nitroprusside with nitroglycerine freshly prepared in the hospital pharmacy and showed that both drugs directly affect vascular smooth muscle and will decrease arterial pressure by a balanced dilation of resistance and capacitance vessels during anaesthesia. They found that coronary perfusion pressure was better maintained by TNG, a conclusion supported by other workers (Chiariello et al., 1976).

In this study, both drugs controlled the intraoperative hypertension by decreasing mean arterial pressure adequately without affecting heart rate or cardiac output, showing that myocardial contractility was unaffected by either agent. The decreases in arterial pressure with both agents were accomplished by decreases in systemic vascular resistance and hence left ventricular afterload. In addition, TNG significantly decreased pulmonary vascular resistance. Left and right ventricular filling pressures were decreased significantly by both drugs. TNG produced a greater reduction in right atrial pressure than SNP which, although statistically significant, was not large enough to be of clinical significance. The decrease in preload reduced left ventricular end-diastolic pressure and decreased ventricular wall tension without substantial alterations in stroke work, suggesting that myocardial oxygen consumption was reduced without impairing cardiac output.

During anaesthesia, no patient exceeded that rate–pressure product which was associated with angina or S-T changes when exercised before operation (table II) and this may explain why only two patients, both in the SNP group, showed S-T depression which disappeared shortly after commencing SNP infusion. Interestingly, these changes were only apparent in the lateral chest lead (V5), demonstrating the importance of monitoring this lead during operation for the detection of ischaemic episodes of the left ventricle (Kaplan and King, 1976).

Nitroglycerine was administered via a plastic giving-set incorporating a burette, and it has been shown that, when used in this way, much of the drug diffuses into the plastic (Cossum et al., 1978). This may explain why doses of TNG required to achieve haemodynamic stability were consistently greater than those reported elsewhere. Absorption may be minimized by infusing TNG using glass syringes coupled with high-density polyethylene connecting tubing. As an alternative the manufacturers could increase the concentration of the agent in the ampoule.

The conclusions to be drawn from this study are that both drugs improve ventricular performance whilst reducing myocardial oxygen consumption, and that there appear to be no clinically important haemodynamic differences between their effects. The change in central venous pressure produced by TNG was significantly greater than that produced by SNP, but the magnitude of the decrease in absolute terms is unlikely to be clinically significant. This opinion is supported by the fact that similar reductions in pulmonary capillary wedge pressure occurred with each agent. Although this study has failed to demonstrate any marked haemodynamic differences between the two drugs, nitroglycerine may be preferred for its more controllable decrease in arterial pressure coupled with less tendency to overshoot.

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COMPARAISON DU NITROPRUSSIATE ET DE LA NITROGLYCERINE POUR CONTROLER L'HYPERTENSION PENDANT UNE INTERVENTION CHIRURGICALE A L'ARTERE CORONAIRE

RESUME

On a comparé sur 22 patients subissant une intervention chirurgicale à l'artère coronaire, les effets hémodynamiques d'une injection de nitroprussiate de sodium à ceux de la trinitroglycérine pour contrôler l'hypertension pendant l'opération. On a pris les mesures nécessaires avant l'induction de l'anesthésie, pendant la sternotomie médiane et au moment où l'on a atteint une diminution stable de la pression artérielle. Ces deux agents ont fait baisser d'une manière significative la pression artérielle sans affecter la fréquence ou le débit cardiaque. La résistance vasculaire systémique, la pression capillaire pulmonaire en coin et le travail systolique ventriculaire gauche et droit ont également diminué. Bien que la nitroglycérine ait fait baisser significativement la résistance vasculaire pulmonaire, et qu'elle ait plus fortement réduit la pression veineuse centrale, ces différences ne semblent pas avoir une importance clinique.

VERGLEICH ZWISCHEN NITROPRUSSID UND NITROGLYZERIN ZUR KONTROLLE VON HYPERTENSION BEI KORONARARTERIENOPERATIONEN

ZUSAMMENFASSUNG

Die hämodynamischen Effekte einer Injektion von Natriumnitroprussid oder von Trinitroglyzerin zur Kontrolle von Hypertension während der Operation wurden an 22 Patienten während Koronararterienoperationen verglichen. Messungen wurden vorgenommen vor Einleitung der Narkose, während der Mediansternotomie und nach Erzielung einer stabilen Senkung des arteriellen Druckes. Beide Drogen senkten den arteriellen Druck deutlich, ohne Herztätigkeit oder Herzminutenvolumen zu beeinflussen. Der systemische Gefässwiderstand, der Lungenkapillardruck und der linke und rechte Ventrikelschlag wurden ebenfalls gesenkt. Obwohl Nitroglyzerin den Lungengefässwiderstand deutlich senkte, und auch eine wesentlich stärkere Senkung des zentralvenösen Druckes bewirkte als Nitroprussid, sind diese Unterschiede klinisch wahrscheinlich kaum von Bedeutung.

COMPARACION DEL NITROPRUSIATO Y DE LA NITROGLICERINA PARA EL CONTROL DE LA HIPERTENSION DURANTE LA OPERACION DE LA ARTERIA CORONARIA

SUMARIO

Los efectos hemodinámicos de la infusión de nitroprusiato de sodio o de trinitroglicerina para controlar la hipertensión durante la operación, se comparó en 22 pacientes sometidos a operación de la arteria coronaria. Se efectuaron mediciones antes de administrar la anestesia, durante la esternotomía mediana y al logro de una disminución estable de la presión arterial. Ambas drogas disminuyeron significativamente la presión arterial sin que el ritmo cardiaco ni la producción cardiaca quedaran afectados. También se disminuyeron la resistencia sistémico vascular, la presión gradual de los capilares pulmonares y el trabajo de bombeo ventricular izquierdo y derecho. Aunque la nitroglicerina disminuyó significativamente la resistencia vascular de los pulmones y produjo una mayor y más significativa disminución en la presión venoso central que el nitroprusiato, no es probable que estas diferencias sean de importancia clínica.

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ELECTROACUPUNCTURE IN THE TREATMENT OF POST-TRAUMATIC SYMPATHETIC DYSTROPHY (SUDECK'S ATROPHY)

C. S. CHAN AND S. P. CHOW

SUMMARY

Twenty patients with established post-traumatic sympathetic dystrophy were treated with electroacupuncture after physical therapy with or without oral medication had failed to produce satisfactory relief of symptoms. Of these patients 14 (70%) experienced marked and permanent improvement. No complications were encountered. The possible mechanisms involved are discussed.

Following injury to an extremity a proportion of patients develop pain, swelling, tenderness, stiffness and vasomotor disturbances in the limb (Mitchell, Morehouse and Keen, 1864; Homans, 1940; Kleinert et al., 1973), an entity commonly called Sudeck's atrophy (Sudeck, 1900) or post-traumatic sympathetic dystrophy. The mechanism involved is poorly understood (Richards, 1967). The intensity of the pain can vary from mild to extremely severe and may result in disability. Many patients recover gradually with physiotherapy and analgesic drugs (Kleinert et al., 1973; Mayfield, 1975). However, in resistant cases, other methods have been advocated, including repeated stellate ganglion block (Kleinert et al., 1973), cervical sympathectomy (Barnes, 1953), regional administration i.v. of a sympatholytic drug (Hannington-Kiff, 1977), and the local continuous instillation of anaesthetics (Omer and Thomas, 1971)—all with varying effects. The purpose of this paper is to report our experience in the use of electroacupuncture in the treatment of this condition.

PATIENTS AND METHODS

In the period May 1978 to December 1979, more than 3000 patients with hand injuries were admitted into the Orthopaedic Unit, Queen Mary Hospital, Hong Kong and 20 developed persistent pain, tenderness, swelling and stiffness of the hand despite at least 1 month of treatment with analgesics and intensive physiotherapy (active exercises, gentle passive mobilization, massage and ice-packs). These patients were assessed by one of the authors (S. P. C.) and it was decided to try acupuncture with electrical stimulation. Physiotherapy was continued.

There was an equal number of men and women and their ages ranged from 24 to 77 yr. The initial injuries included fractures (nine patients), crushed hands (four patients), lacerations or cuts (four patients) and sprain (three patients). Electroacupuncture was started 1–6 months following the initial injury and was carried out by one of the authors (C. S. C.) as follows. The written consent of the patient was obtained after careful explanation of the technique. All acupuncture needles were autoclaved. They were inserted through the skin after preparation of the skin with antiseptic. Acupuncture loci were used for the insertion of the needles, as it is well known that the loci are associated with nerves or rich nerve endings. Only loci on the affected limb were used. However, the loci used were not selected as precisely as recommended in the Chinese acupuncture texts, but based on a knowledge of the regional innervation, and at the site of maximal complaint. Four loci were used at each session of treatment. After insertion the needles were grouped into two pairs, so that each pair lay along the course of a regional nerve or blood vessel. The needles were connected to a stimulator which was powered by a 9-V dry battery. A monophasic electrical pulse of 50 Hz was passed for 20–30 min. Pulse duration was 0.4 ms. The intensity of the current was adjusted to give maximal stimulation without discomfort or pain. Altogether 5 to 10 sessions were given to each patient, on either consecutive or alternate days.

The range of movement of joints and the power of gripping and pinching were assessed by an

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occupational therapist both before and after treatment. The degree of swelling and the extent of erythema and tenderness were noted. The patient's subjective assessment of the degree of pain relief was graded as "marked" (with complete relief or two-thirds of pain relieved), "some" (between one-third to two-thirds of relief), and "nil" (with less than one-third improvement).

RESULTS

Immediate results

No patient became worse after acupuncture and there were no complications. Improvement usually became evident after the third session of treatment. The degree of pain relief obtained is presented in table I. The two patients who did not respond to treatment had a fracture of the lower end of the radius with laceration of the median nerve, and a badly crushed forearm with adhesions around the nerve.

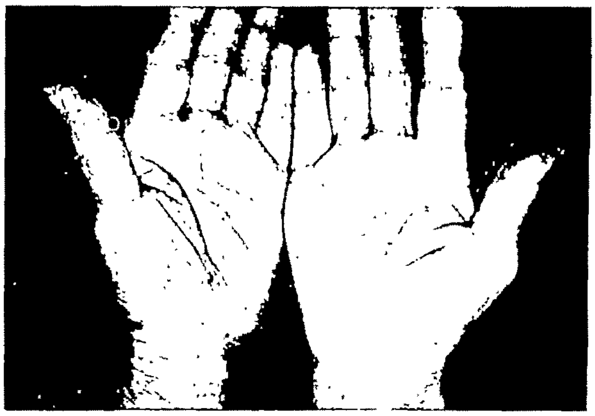

FIG. 2. Showing the same hands after the sixth session of electroacupuncture (8 days after initiation of treatment). Reduction of swelling of the left hand is indicated by wrinkling of skin.

TABLE I. *Subjective improvement in pain relief at end of course of electroacupuncture*

	Worse	No improvement	Some improvement	Marked improvement
Number of patients	0	2 (10%)	4 (20%)	14 (70%)

Alterations in the power of gripping and pinching, before and after electroacupuncture, were recorded in 10 patients. Nine had marked subjective decrease in pain, and in eight muscle power improved markedly. The remaining patient had no subjective decrease in pain and muscle power showed a minimal increase. The correlation between subjective relief of pain and increase of muscle power was good.

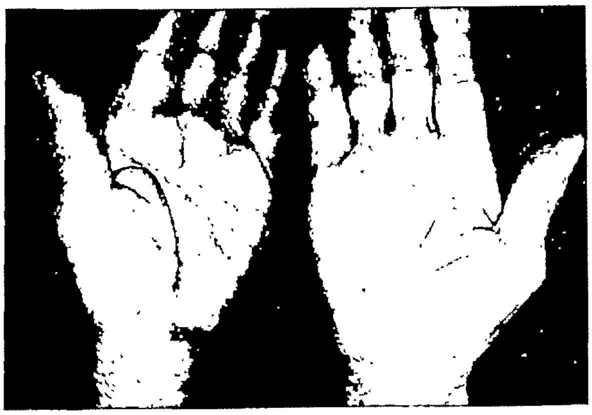

FIG. 1 Showing the hands of a patient before electroacupuncture, the left hand being markedly swollen after a Colles fracture 2 months previously. The fracture had been reduced and union was good.

On the other hand, the improvement in range of movement was unimpressive. Of 10 patients in whom the range of movement was recorded, only three showed any improvement.

Swelling was decreased to a variable degree, indicated by wrinkling of skin (figs 1 and 2). Erythema decreased at the same time.

Late results

In March 1980, the condition of the patients was re-assessed, that is from 3 to 22 months after electroacupuncture. Information on 17 patients was obtained. All the patients showing "marked" and "some" pain relief initially had either retained this degree of improvement or had improved further.

Of the two patients showing no improvement initially, one had an exploration which revealed a badly lacerated median nerve at the wrist. The other patient had died in a fire.

DISCUSSION

Acupuncture loci may be located by variations in d.c. skin conductance (Reichmanis, Marino and Becker, 1976) and since many acupuncture loci are distinct local conductance maxima they can be determined objectively. However, not all acupuncture loci may be objectively determined. It is recommended that the method of loci location described above be used for the selection of points for acupuncture, including the point(s) at the site of maximum discomfort.

The passage of the electric current during electroacupuncture may act locally to relax the post-capillary sphincters, thus improving the local circulation and thereby relieving local oedema and swelling. That the relief of pain in these patients should be improved is not difficult to understand from the recent discovery of endogenously released morphine-like substances. Acupuncture stimulation sends ascending impulses to the brain, causing release of endorphins and encephalins. These are bound to specific morphine receptors located in the periaqueductal grey area, resulting in activation of a descending inhibitory pain pathway which modulates pain transmission (Bonica, 1977; Yang and Kok, 1979). Since most Chinese patients have faith in acupuncture as a form of therapy, psychogenic factors play a role also.

Once the pain decreased the patients started to exercise more actively, thus decreasing the oedema and stiffness. The vicious cycle of post-traumatic sympathetic dystrophy was broken; the power of grip and pinch improved. However, the range of movement had not improved significantly at the end of treatment. This is not surprising since, in a hand injury, injury to bone, tendon and scarring can cause stiffness apart from the pain and swelling and even in those patients without these concomitant injuries, stiffness may take several weeks to resolve.

Only two patients (10%) in this series showed improvement of less than 33% and were noted as showing no improvement because a placebo could achieve a similar result (Beecher, 1959). One of these patients was found to have a lacerated median nerve at the wrist which probably explained why electroacupuncture failed. The overall result of "marked" improvement in 70% of patients and "some" improvement in another 20% was remarkable and compared favourably with the results from other methods of treatment of this condition (Omer and Thomas, 1971; Kleinert et al., 1973).

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ELECTROACUPUNCTURE POUR LE TRAITEMENT DE LA DYSTROPHIE SYMPATHIQUE POSTTRAUMATIQUE (ATROPHIE DE SUDECK)

RESUME

On a traité vingt patients souffrant de dystrophie sympatique posttraumatique reconnue par électroacupuncture après que la thérapie physique, avec ou sans médicament administré par voie buccale, ait échoué dans la production d'un soulagement satisfaisant des symptômes. Quatorze patients sur les vingt, soit 70%, ont été nettement soulagés et ce d'une manière permanente. On n'a rencontré aucune complication. On décrit dans cet article les méchanismes qui sont probablement entrés en jeu.

ELEKTROAKUPUNKTUR BEI DER BEHANDLUNG VON POST-TRAUMATISCHER SYMPATHETISCHER DYSTROPHIE (SUDECK-ATROPHIE)

ZUSAMMENFASSUNG

Zwanzig Patienten mit post-traumatischer sympathetischer Dystrophie wurden mit Elektroakupunktur behandelt, nachdem physikalische Therapie mit oder ohne oral verabreichten Medikamenten die Symptome nicht auf zufriedenstellende Weise behoben hatte. Vierzehn dieser Patienten (70%) zeigten deutliche und permanente Besserung. Keine Komplikationen traten auf. Die hier beteiligten möglichen Mechanismen werden diskutiert.

ELECTROACUPUNTURA EN EL TRATAMIENTO DE LA DISTROFIA SIMPATICA Y POSTRAUMATICA (ATROFIA DE SUDECK)

SUMARIO

A veinte pacientes con distrofia simpática y postraumática se les trató con electroacupuntura, después de que la fisioterapia, con o sin medicamentos orales, hubiera fracasado en producir un alivio satisfactorio de los sintomas. Catorce de estos pacientes (70%) experimentaron una marcada y permanente mejoria. No se encontraron complicaciones. Se discuten los posibles mecanismos involucrados.

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PULMONARY EMBOLISM DURING SURGERY FOR A WILMS' TUMOUR (NEPHROBLASTOMA)

Case Report

M. G. AKYÖN AND G. ARSLAN

SUMMARY

During resection of a Wilms' tumour in a 10-year-old girl, sudden bradycardia, hypotension and cyanosis developed, leading to cardiac arrest. It was thought that part of the tumour had caused a pulmonary embolus. After prompt resuscitation, cardiopulmonary bypass surgery was started within 20 min. At operation the left pulmonary artery was blocked by a tumour embolus which was removed with a Fogarty catheter. The patient is still alive and well 27 months after her operation. We believe her to be the longest surviving patient of this type.

Pulmonary emboli can be recognized clinically, depending on their size and location. Postmortem examinations show that the rate of pulmonary embolism in adults is high, but that massive pulmonary embolism in children is rare.

Pulmonary emboli usually originate from venous thrombosis in the legs or pelvis, but air, fat, tumours and amniotic fluid can also cause pulmonary embolism. Pulmonary embolism following venous catheterization has occurred following damage to the catheter or vein.

We report pulmonary embolism during resection of a Wilms' tumour. The tumour had invaded the renal vein and became detached during resection.

CASE REPORT

A 10-year-old girl was admitted to the Department of Paediatrics at Hacettepe University Medical Faculty Hospital on February 12, 1979. Her family had first noticed abdominal distension 4 months earlier, but had not thought it to be important. Eventually she developed nausea, vomiting and diarrhoea. Her previous medical history was unremarkable. Physical examination revealed a 10 × 15 cm immobile mass in the left hypochondrium, and a second mass 10 cm in diameter which was mobile and lay medial to the first. Laboratory findings were normal. An i.v. pyelogram showed no infiltration. A liver and spleen scan showed reduced uptake in an area 6 × 6 cm. A diagnosis of Wilms' tumour was made and laparotomy planned for the following day.

One hour before operation the patient received i.m. pethidine 30 mg and atropine 0.3 mg. Anaesthesia was induced with thiopentone 150 mg and the trachea was intubated following suxamethonium 30 mg. Anaesthesia was maintained with oxygen 3 litre min^{-1}, nitrous oxide 4 litre min^{-1} and halothane 1%.

For the first 35 min of the operation, the heart rate and arterial pressure were stable. At this point, the tumour was removed and the patient developed a bradycardia which responded to atropine 0.25 mg i.v. While the tumour was being removed, it was noticed that it had invaded the renal vein and this was clamped close to the inferior vena cava. When the clamp was removed to allow resection of the tumour tissue invading the vein the surgeon noticed that part of the tumour had entered the inferior vena cava. Bearing in mind the likelihood of pulmonary embolism and the possible need for cardiopulmonary bypass, the surgeon quickly secured haemostasis and started to close the abdomen.

Towards the end of the operation, the patient's arterial systolic pressure decreased to 40 mm Hg, bradycardia recurred and she became cyanosed. After ephedrine 15 mg i.v., the systolic pressure increased to 90 mm Hg, but the cyanosis increased despite breathing 100% oxygen. Cardiac arrest followed and external cardiac massage was commenced. Atropine 0.5 mg was given i.v. and the heart restarted with a systolic pressure of 50 mm Hg and a heart rate of 140 beat min^{-1}. While the abdomen was being closed, preparation

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was made for thoracotomy and cardiopulmonary bypass.

Twenty minutes after the cardiac arrest the patient's chest was opened. At this time she was cyanosed and the arterial pressure was unmeasureable. On opening the pericardium, the right ventricle and main pulmonary artery were found to be dilated by increased pressure. After starting cardiopulmonary bypass with moderate hypothermia (32 °C), pulmonary arteriotomy was performed. A piece of tumour ($4 \times 3.5 \times 1$ cm) was removed from the left pulmonary artery with a Fogarty catheter. The right pulmonary artery was clear and the pulmonary artery was closed. After discontinuation of cardiopulmonary bypass, the patient's heart and pulmonary artery returned to a normal size. The systolic arterial pressure was 90 mm Hg, heart rate 140 beat min^{-1}, CVP $+11$ cm H_2O and the patient was no longer cyanosed. Sodium bicarbonate 10 mmol and dexamethasone 8 mg were given and the chest was closed.

After operation the patient was digitalized and received IPPV (Bird ventilator) in the intensive care unit. Blood-gas analysis showed Pa_{O_2} 36.5 kPa, Pa_{CO_2} 3.2 kPa and pH 7.40. The tracheal tube was removed 4 h after operation.

On the 2nd day after operation the arterial systolic pressure was 110 mm Hg, heart rate 120 beat min^{-1} and CVP $+12$ cm H_2O. Pa_{O_2} was 13.1 kPa, Pa_{CO_2} 2.9 kPa and pH 7.46. Four days after operation the patient was transferred to the ward. She developed pyrexia 2 days later and this lasted 10 days despite antibiotic treatment. No clinical or radiological lung disorder was detected.

The patient was discharged home on March 21, after which she received a course of radiotherapy and chemotherapy.

Twenty-seven months later she is alive and well with no sign of recurrence.

DISCUSSION

Wilms' tumour (nephroblastoma) is the commonest abdominal tumour in children. It is a malignant tumour of embryonic origin, developing from the mesoderm of the intermediate cell mass before it differentiates. It has been found in newborn infants, but usually presents a few years later. It has been reported that 39% of Wilms' tumours invade the renal vein but, although the tumour can reach the inferior vena cava and the right atrium, this is relatively rare (Anselmi et al., 1970). There was no inferior vena caval obstruction in our patient. When tumour is found in the inferior vena cava the frequency of massive pulmonary embolism is high (Emery, 1962; Arthur et al., 1973).

Kontecky reported a case of fatal massive pulmonary embolism during resection of a Wilms' tumour (Kontecky, Bonsko and Stejskal, 1978). A similar death under anaesthesia occurred when an 18-month-old girl with a vaginal tumour was being examined (Arthur et al., 1973). Postmortem examination showed that the tumour extended through the right iliac artery into the inferior vena cava, and a tumour embolus had obstructed the main pulmonary artery. Utley and others (1973) reported a case similar to our own, occurring during operation on an adult with a Wilms' tumour. When the heart was opened, a piece of tumour was found obstructing the tricuspid valve. The patient survived the operation, but died 3 months later from pneumonia.

Twenty-seven months after operation our patient is still well. We believe this to be the first long-term survivor following massive pulmonary embolism during resection of a Wilm's' tumour.

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EMBOLIE PULMONAIRE PENDANT UNE INTERVENTION CHIRURGICALE POUR UNE TUMEUR DE WILMS (NEPHROCHONDROME):

Rapport sur un cas particulier

RESUME

Pendant la résection d'une tumeur de Wilms effectuée sur une petite fille de 10 ans, on a soudain constaté une bradycardie avec hypotension et cyanose, qui a entraîné un arrêt cardiaque. On a pensé qu'une partie de la tumeur avait causé une embolie pulmonaire. Après une prompte réanimation, on a, dans les 20 min qui ont suivi, effectué une dérivation cardiopulmonaire. Lors de l'opération, on a trouvé que l'artère pulmonaire gauche

avait été bloquée par une embolie tumorale que l'on a enlevée à l'aide d'un cathéter de Fogarty. La patiente est toujours en vie et se porte bien 27 mois après son opération. Nous croyons qu'elle est la patiente qui a survécu le plus longtemps à une opération de ce genre.

LUNGENEMBOLIE BEI OPERATION AN EINEM WILMS-TUMOR (NEPHROBLASTOM)

ZUSAMMENFASSUNG

Während der Resektion eines Wilms-Tumors bei einem 10-jährigen Mädchen entwickelten sich plötzlich Bradykardie, Hypotension und Cyanose, was zu Herzversagen führte, Man nahm an, dass ein Teil des Tumors einen Lungenembolus verursacht hatte. Nach prompter Wiederbelebung wurde innerhalb von 20 Minuten ein Eingriff bei Herz/Lungen-Bypass vorgenommen. Es zeigte sich, dass die linke Lungenarterie durch einen Tumor-Embolus blockiert war, der nun mit einem Fogarty-Katheter entfernt wurde. Die Patientin ist jetzt, 27 Monate nach der Operation, immer noch am Leben. Wir halten sie für die am längsten überlebende Patientin dieser Art.

EMBOLISMO PULMONAR DURANTE OPERACION QUIRURJICA RELATIVA A UN TUMOR DE WILMS (NEFROBLASTOMA)

Informe al caso

SUMARIO

Durante la extirpación de un tumor de Wilms en una muchacha de 10 años de edad se desarrollaron repentinamente bradicardia, hipotención y cianosis concluyendo en la paralización del corazón. Se pensó que parte del tumor había ocasionado un émbolo pulmonar. Después de la rápida resucitación se inició, al cabo de 20 minutos, la operación quirúrjica de desviación cardiopulmonar. Durante la operación la arteria pulmonar izquierda quedó bloqueada por un émbolo del tumor, el cual se extrajo mediante un catéter de Fogarty. La paciente sigue viva y sana después de 27 meses de la operación. Consideramos que dicha paciente es la que más ha sobrevivido a este tipo de intervención quirúrjica.

Br. J. Anaesth. (1981), 53, 907

CORRESPONDENCE

NEOSTIGMINE AND ATYPICAL PLASMA CHOLINESTERASE ACTIVITY

Sir,—Neostigmine has been shown to inhibit the plasma cholinesterase in patients having normal enzyme activity (Baraka et al., 1981). We report the inhibitory effect of neostigmine in two patients inheriting atypical cholinesterase compared with the response of a group with normal enzyme activity. One of the two atypical patients was heterozygote while the second was a homozygote. The plasma cholinesterase activity and the dibucaine numbers of patients are shown in table I.

TABLE I. *The serum cholinesterase activity and the dibucaine number in the control group of patients having normal cholinesterase activity (Baraka et al., 1981) and in the two patients having heterozygote and homozygote atypical activity*

	Control	Heterozygote	Homozygote atypical
Cholinesterase activity (iu litre^{-1})	264.6 (SEM 21.7)	152	50
Dibucaine no.	73–90	60	20

The effect of neostigmine 0.05 mg kg^{-1} on the plasma cholinesterase activity in the two atypical patients compared with the normal group is shown in figure 1, while the percentage inhibition of enzyme activity is shown in figure 2. The absolute amount of enzyme depression following neostigmine was less in the atypical homozygote patient than that observed in the heterozygote patient or the control group (fig. 1). However, the percentage depression of enzyme activity was essentially similar in degree and duration (fig. 2).

The inhibitory effect of neostigmine on normal, heterozygote or atypical cholinesterase activity may explain the effect of neostigmine on suxamethonium block in such patients. In patients with normal plasma cholinesterase activity, the enzyme determines the rate of hydrolysis of suxamethonium (Kalow, 1959). Suxamethonium will be rapidly hydrolysed, resulting in a short-lasting neuromuscular block. Neostigmine, which inhibits plasma cholinesterase, has been shown to potentiate the neuromuscular block of suxamethonium in patients with normal enzyme activity, whether the block is depolarizing or desensitizing in nature (Baraka, 1977). Injection of different doses of neostigmine causes a dose-related decrease in plasma cholinesterase activity, which in turn is followed by a dose-related increase in duration of action of suxamethonium (Jørgensen et al., 1980). In patients with homozygote atypical cholinesterase activity, the enzyme plays virtually no role in the hydrolysis of suxamethonium in the doses used clinically (Kalow, 1959), and hence suxamethonium produces a very prolonged neuromuscular block. Further inhibition of enzyme activity by neostigmine will affect the rate of hydrolysis minimally, if at all. However, the anti-acetylcholinesterase activity of neostigmine may predominate in atypical patients, and the acetylcholine accumulated at the endplate can therefore potentiate the depolarizing phase of suxamethonium block, but can reverse the desensitizing phase. The degree of reversal depends on the degree of desensitization (Baraka, 1977). In patients with homozygote atypical cholinesterase, neostigmine can prolong markedly the neuromuscular block of suxamethonium, if given too early before the desensitizing phase is fully established (Bush, 1961; Vickers, 1963; Baraka, 1975, 1977). In heterozygote atypical patients with intermediate cholinesterase activity, moderately prolonged neuromuscular block may follow suxamethonium (Viby-Mogensen and Hanel, 1980). Heterozygotes become more sensitive to suxamethonium whenever a quantitative decrease

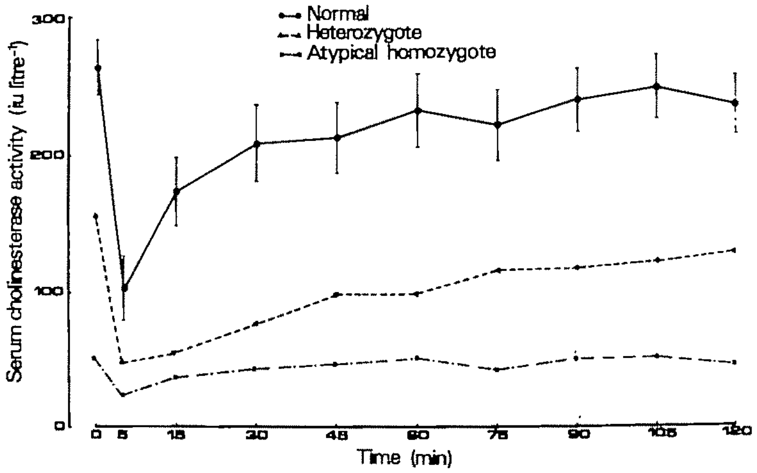

FIG. 1. Effect of neostigmine 0.05 mg kg^{-1} on serum cholinesterase in the two patients with heterozygote and homozygote atypical activity and in the normal group (mean ± SEM).

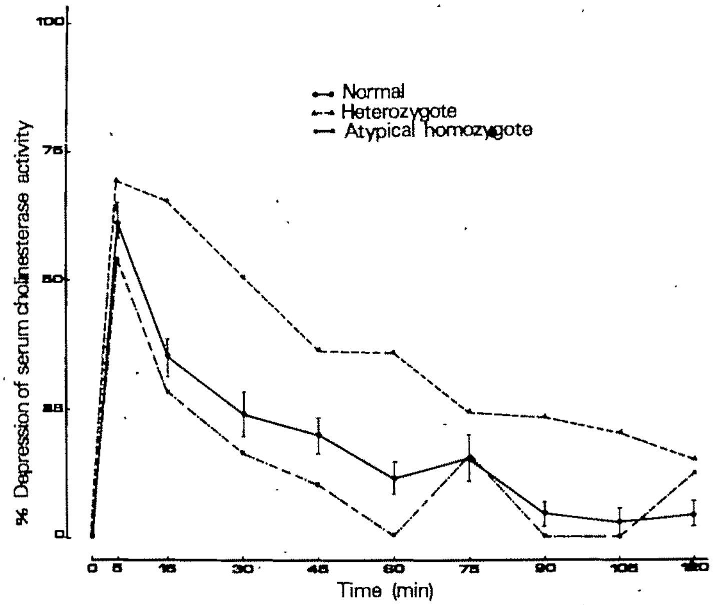

FIG. 2. Percentage depression of serum cholinesterase activity following neostigmine 0.05 mg kg^{-1} in the two patients with heterozygote and homozygote activity compared with the normal group (mean ± SEM).

in cholinesterase activity is observed, as in liver disease, cancer and in the last trimester of pregnancy (Whittaker, 1980). In heterozygotes, neostigmine can also reduce the plasma cholinesterase activity to very low levels, comparable to that obtained in homozygote atypical patients, and hence may markedly potentiate suxamethonium block.

It appears that the effect of neostigmine on suxamethonium block will vary with different genotypes of serum cholinesterase and the nature of the neuromuscular block. In patients with normal or heterozygote cholinesterase activity, neostigmine will potentiate suxamethonium block irrespective of its nature. In patients with atypical homozygote activity, neostigmine will potentiate the depolarizing phase of the block and antagonize its desensitizing phase. Because of the complexity of these factors, it is wiser to avoid the use of neostigmine in all patients, for reversal of prolonged suxamethonium block. Adequate patience is the best and least toxic therapeutic agent (Vickers, 1963).

ANIS BARAKA
Beirut, Lebanon

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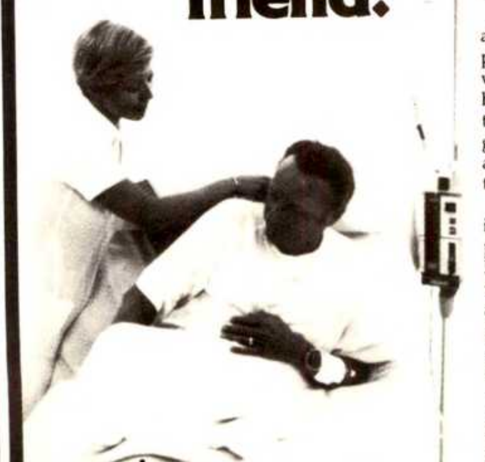

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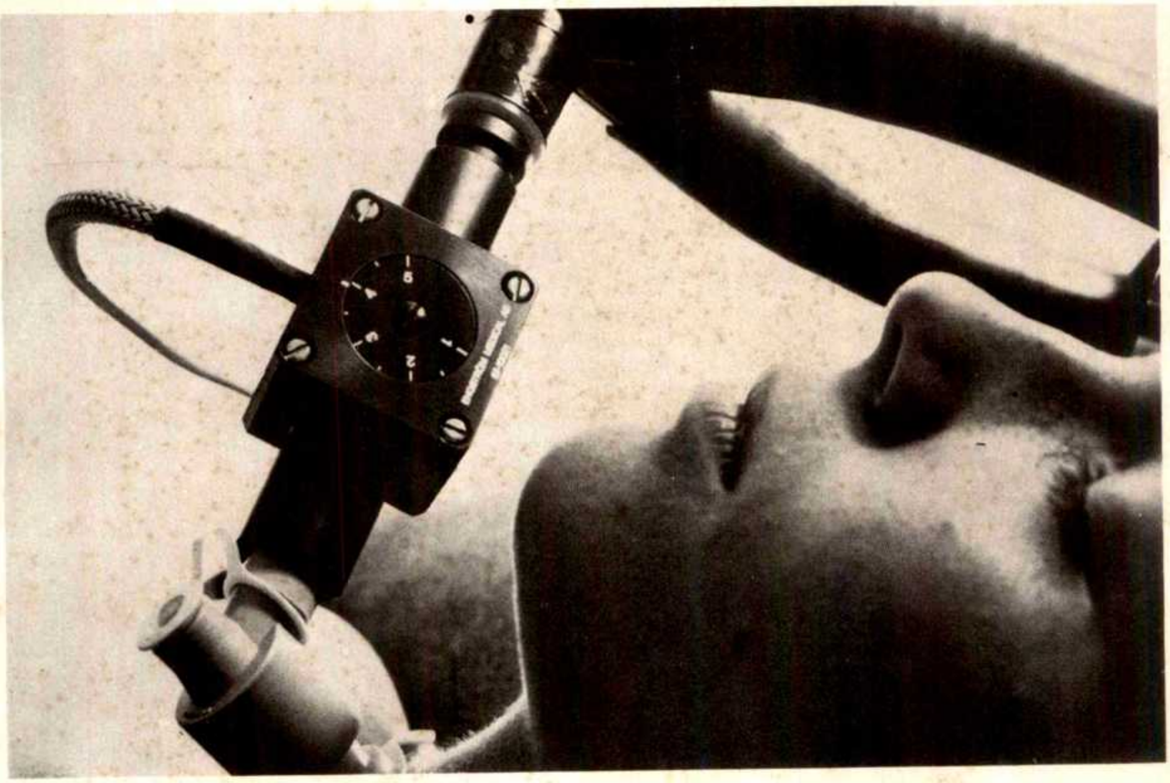

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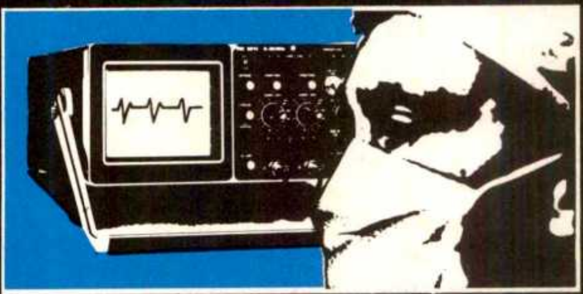

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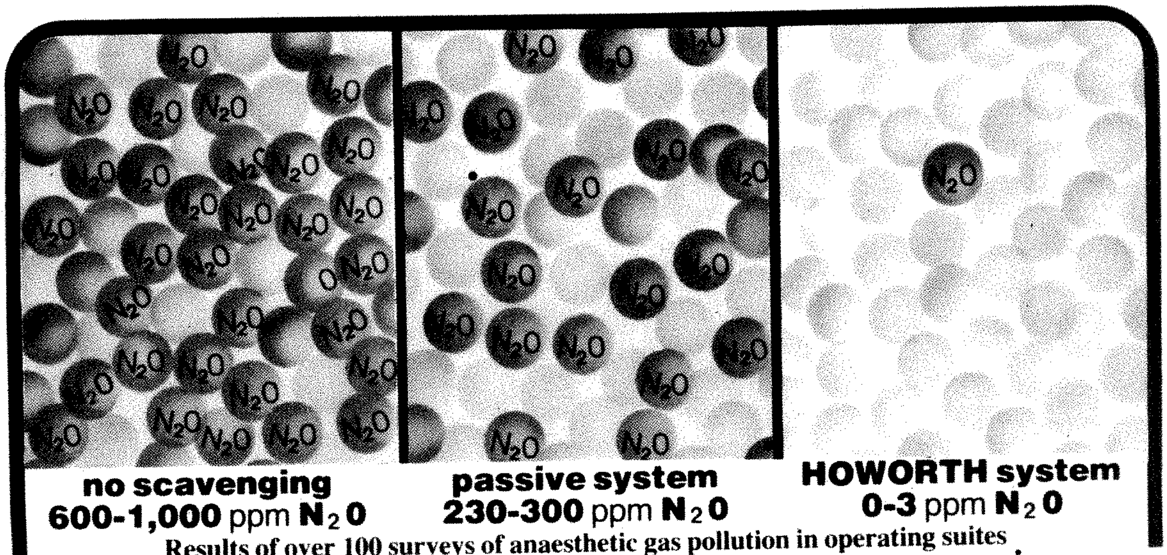

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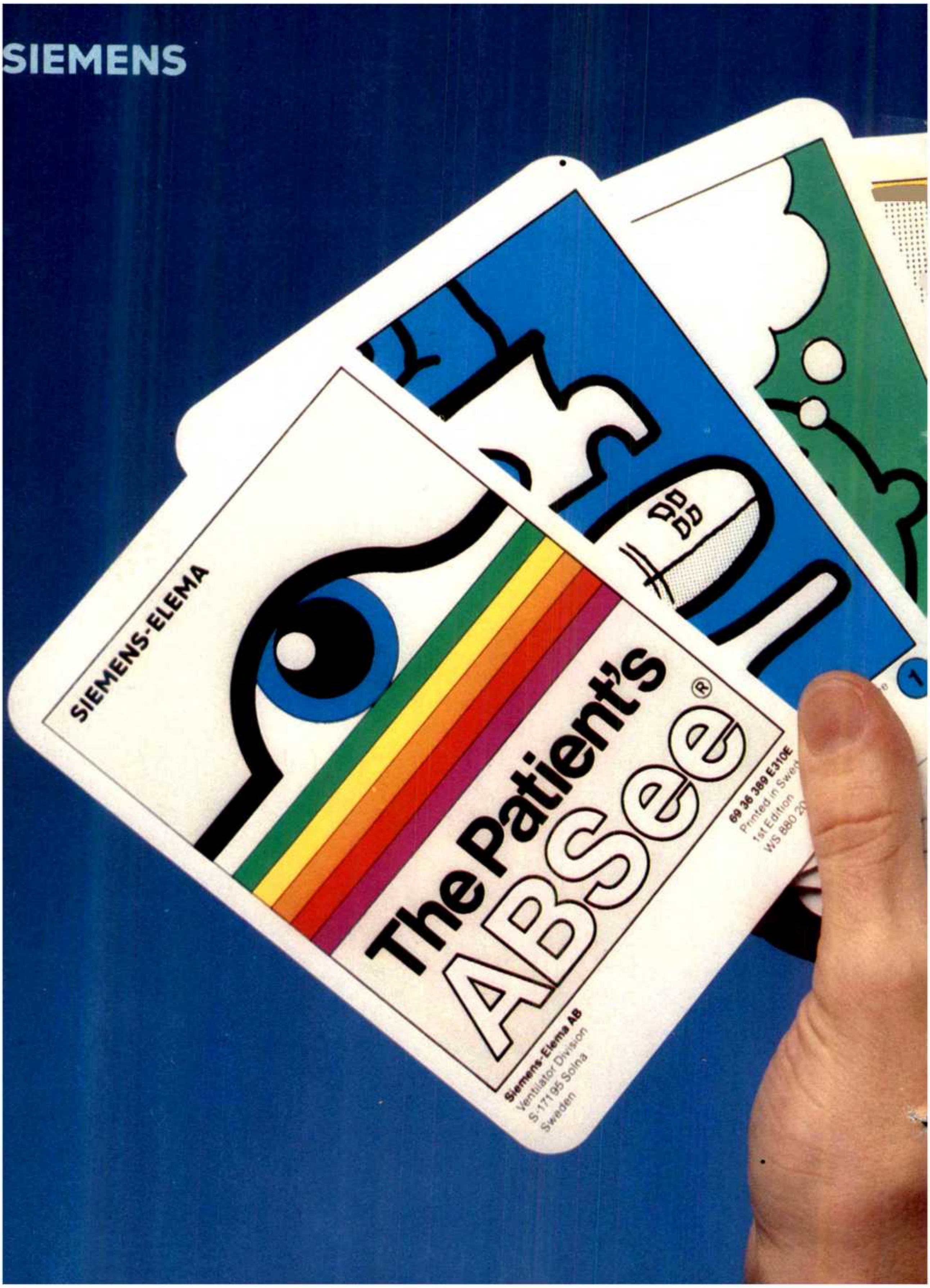
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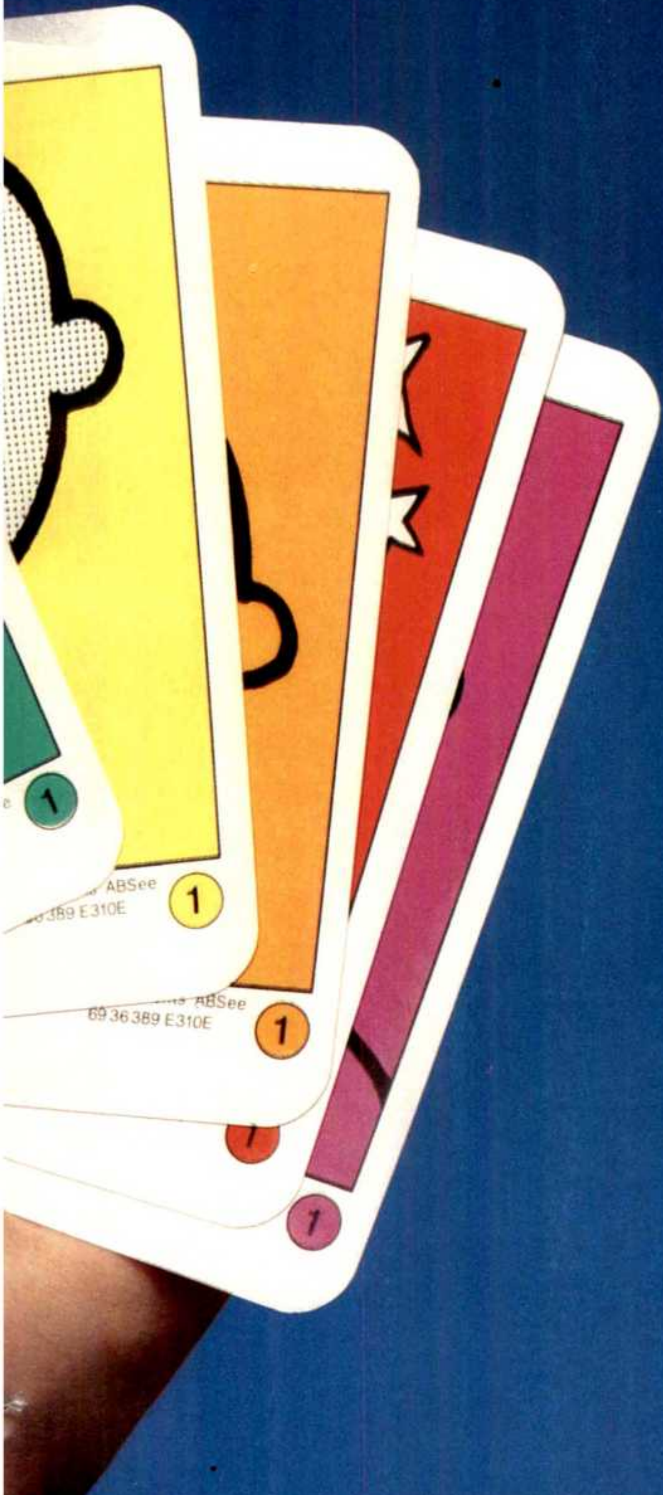

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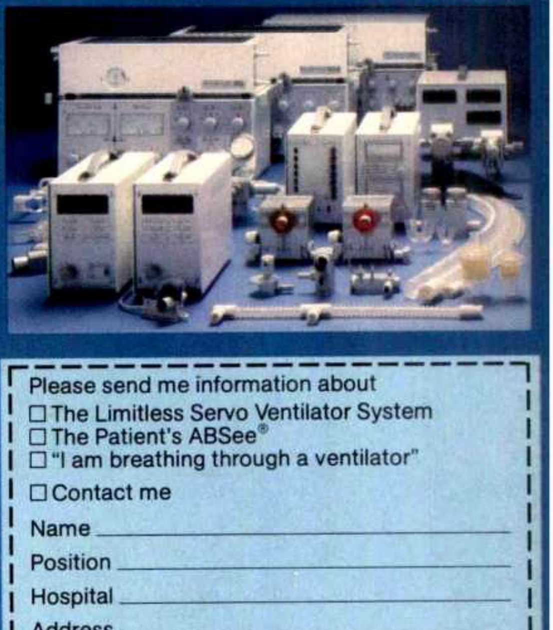

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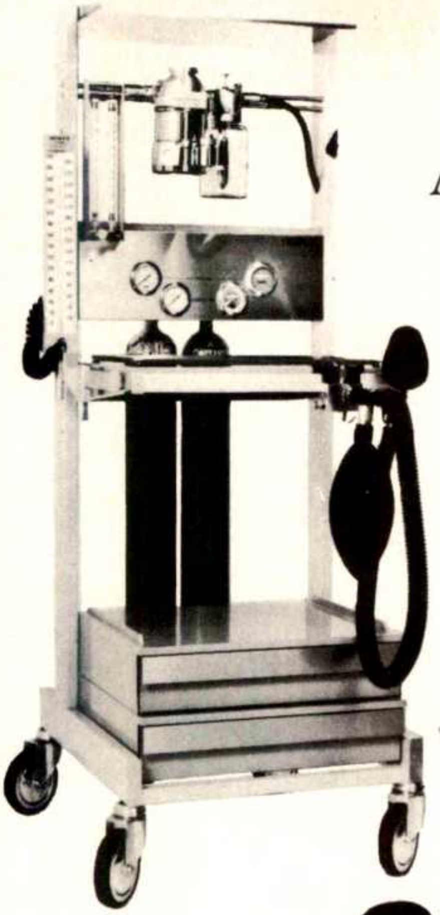

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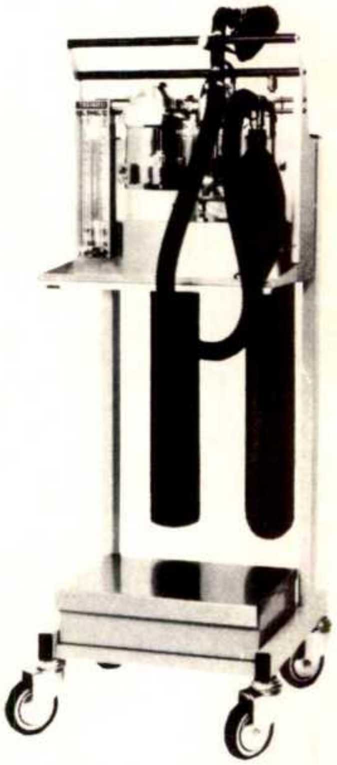

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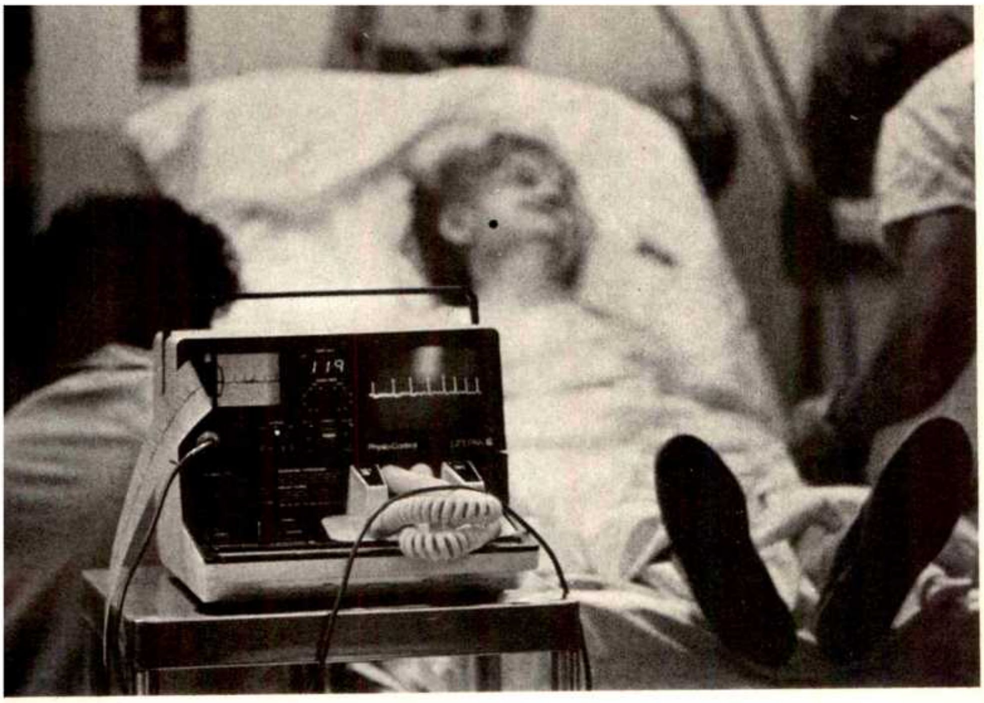

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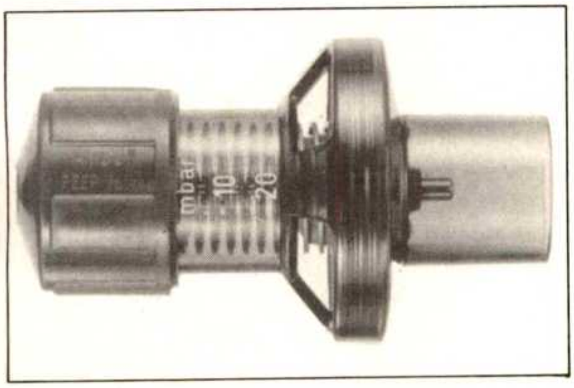

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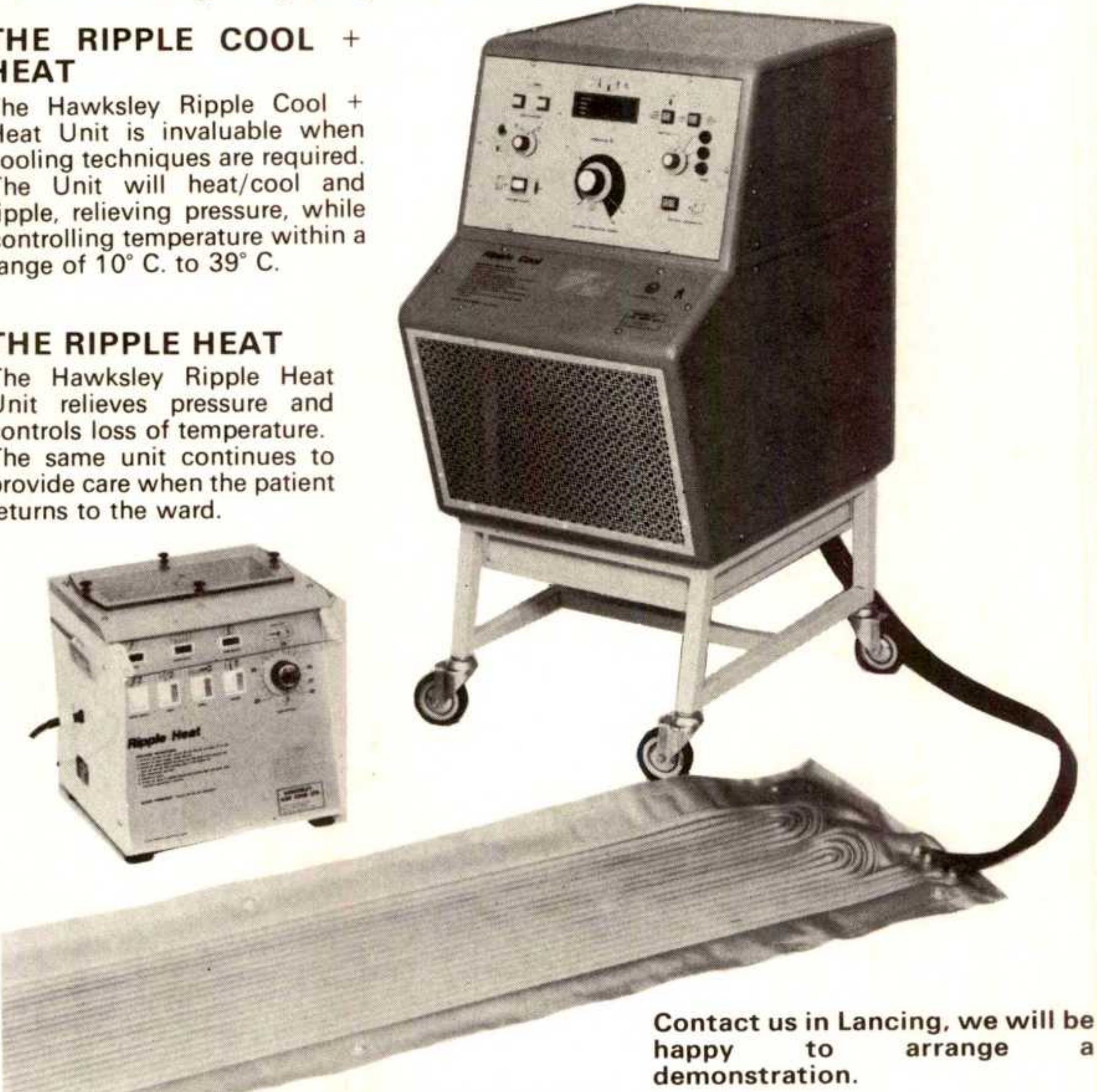

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1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

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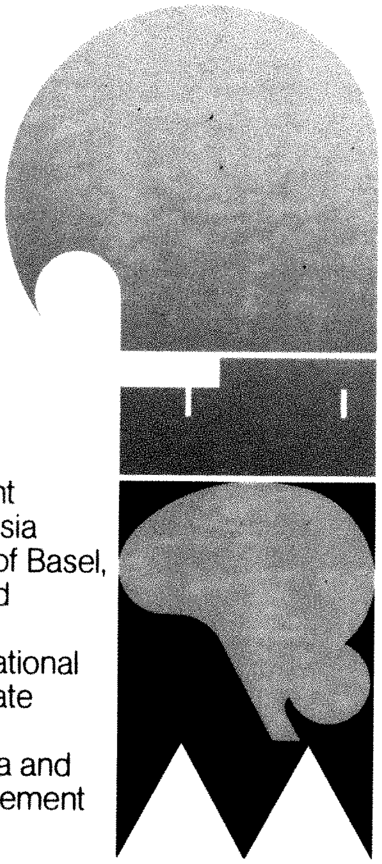

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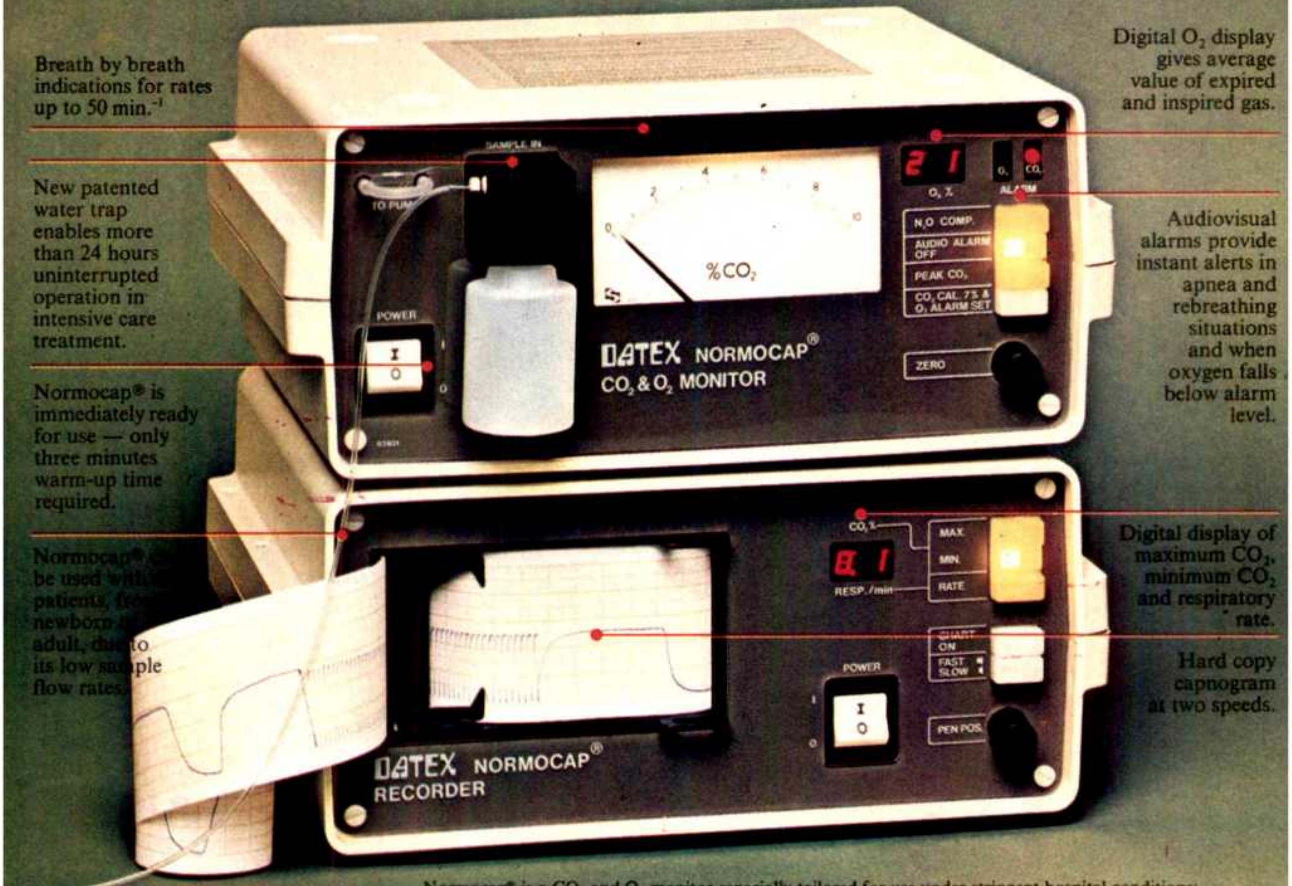

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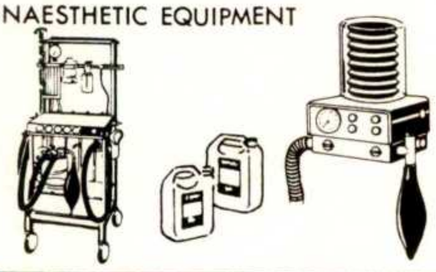

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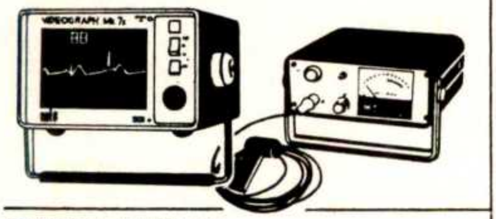

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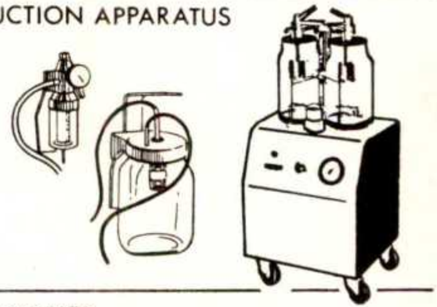

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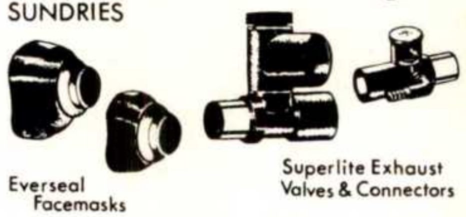

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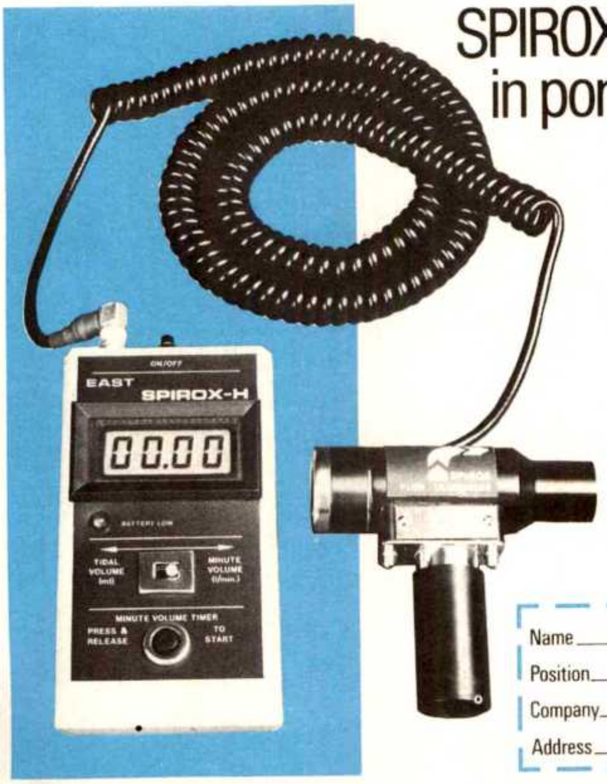

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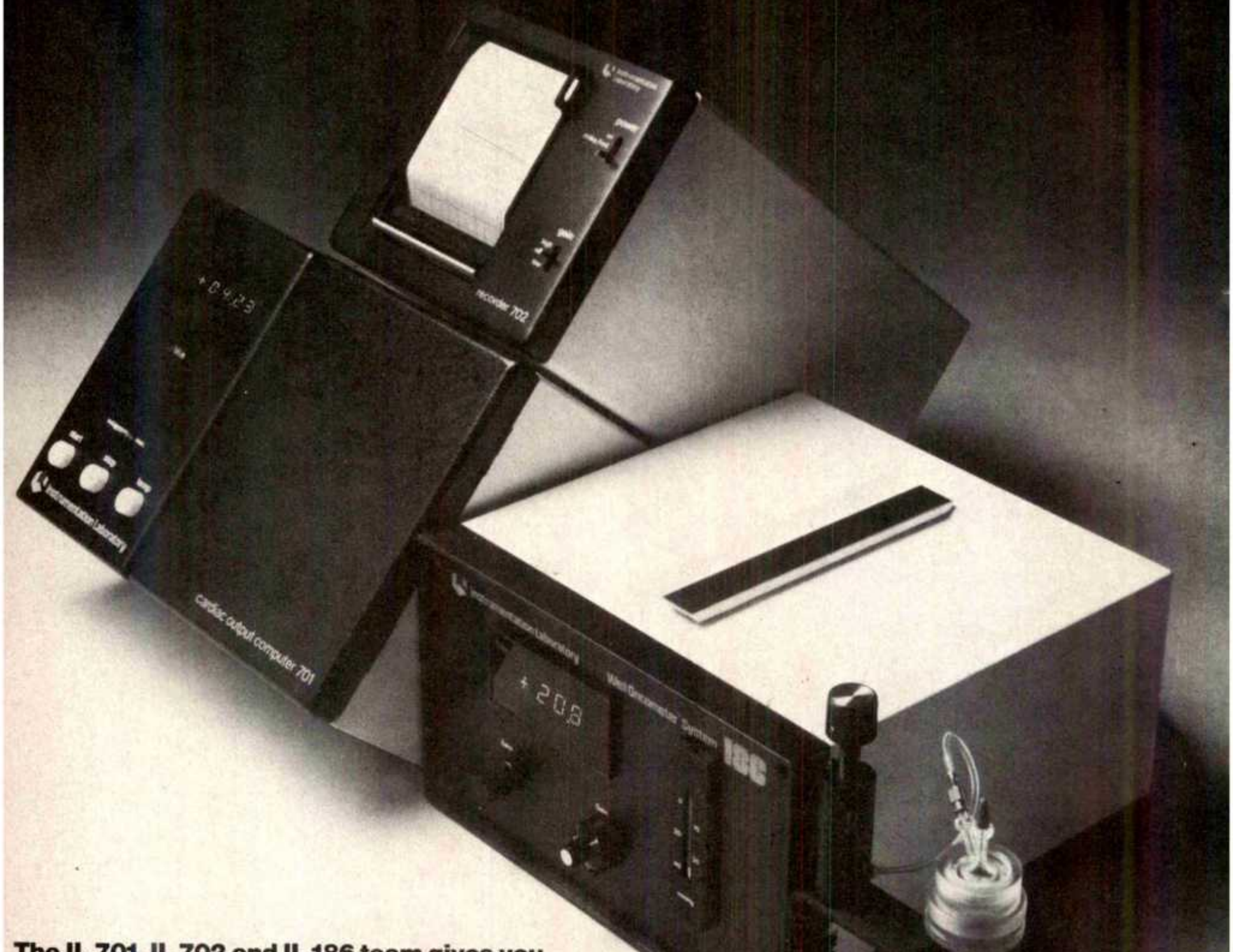
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2. Kamel, M.M. and Geddes, I.C. (1978) *Br. J. Br. J. Anaesth*, **50**, 599.
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4. Data on file, Reckitt & Colman Pharmaceutical Division.

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EDITORIAL

CHANGING ASPECTS OF THE CEREBRAL CIRCULATION

For almost one hundred years it has been assumed that the circulation of the brain is modulated, at least in part, by the products of cerebral metabolism and that under physiological conditions blood flow is adjusted by local metabolic and functional activity. However, definitive evidence in support of this assumption has been obtained only recently with the development of techniques which permit the measurement of local cerebral blood flow and local cerebral energy metabolism in discrete anatomical areas of the brain. That it is now possible to study with precision, local cerebral blood flow and relate this to local cerebral metabolism and functional activity was amply demonstrated in many of the contributions presented at the Tenth International Symposium on Cerebral Blood Flow and Metabolism which was held in St Louis, Missouri from June 19–23, 1981.

The first of these Symposia was held in Scandinavia in 1965 and since then they have been the focal point for the presentation and discussion of investigations in this field. An analysis of the principal contents of three of those Symposia (table I) provides a picture of the change in emphasis which has taken place. Initially, emphasis was on the cerebral circulation itself: the structure and innervation of the blood vessels, the precise regulation of blood flow, "autoregulation" and its possible mechanisms and the changes induced by significant alterations in physiological variables such as arterial pressure, oxygen tension and carbon dioxide tension. In addition, the effects of pharmacological agents and in particular, anaesthetic drugs, were assessed. As a result the basic physiological "economy" of the brain was defined and the principles applied in many areas of clinical practice, not least anaesthesia.

It is obvious that interest in the cerebral circulation (the actual plumbing of the brain) is decreasing while that in flow mapping, flow–metabolism coupling and the effects of functional activity on both flow and metabolism is increasing. This is not surprising, for there is no doubt that the ability to measure local cerebral blood flow and local metabolic activity using autoradiography in animals and positron emission tomography in man provide new and powerful tools with which to study the brain. Approximately 300 contributions were presented in St Louis of which about one-third described investigations using these new imaging techniques.

Three matters call for comment. There is a real danger that the cart will be put before the horse—that the technology will advance in response to technical innovation rather than in the attempt to solve clinical problems.

The early investigations on the cerebral circulation are the foundation of our understanding of the physiological function of the brain and of the effects of pharmacological agents. The present studies will undoubtedly increase our knowledge in these fields. However, it should not be lost sight of that, as anaesthetists, we have still a lot to learn about how the cerebral circulation responds and reacts during anaesthesia and surgery, in the period following operation and under the clinical and pharmacological "insults" of intensive therapy. These areas of interest would appear to be those for which an established inert-gas clearance technique with simple external counting remains the most appropriate and has still much to offer.

It was disappointing to realize that, at this most recent Symposium there was no session devoted to anaesthesia and, indeed, only three papers dealing

TABLE I. *Principal sessions during three Symposia*

1973 (Sixth Symposium)
1. Autoregulation
2. Chemical Control
3. Focal Lesions I
4. Focal Lesions II
5. Methodology I
6. Diffuse Ischaemia I
7. Diffuse Ischaemia II
8. ICP and CBF
9. Clinical Stroke
10. Clinical Miscellaneous
11. Pharmacology and Anaesthesia
12. CBF and Electrical Activity
13. Methodology II
14. Neurogenic Control I
15. Neurogenic Control II
16. Neurogenic Control III
17. Metabolism

1977 (Eighth Symposium)
1. Neurogenic Control
2. Autoregulation
3. Biogenic Amines I
4. Biogenic Amines II
5. Ischaemia
6. Recovery
7. Barbiturate Therapy
8. Stroke
9. Atraumatic Methods
10. Migraine
11. Metabolic Control
12. Epilepsy
13. Deactivation
14. Activation I

(15).

16. Neurogenic Mechanisms
17. Vasospasm
18. Subarachnoid Haemorrhage
19. Neurochemistry
20. Infarction
21. Brain Vessel
22. Cerebrovascular Disease
23. Newborn: Platelets
24. New Methods
25. Xenon Inhalation
26. Blood–Brain Barrier
27. Neurosurgery: Neuroanaesthesia
28. Oedema—ICP

1981 (Tenth Symposium)
1. Autoradiography: Studies in Man
2. Autoradiography: Studies in Animals
3. Experimental Metabolism
4. Experimental Cerebral Ischaemia
5. Prostaglandins
6. Neurogenic Control
7. Blood–Brain Barrier
8. Higher Cortical Function
9. Cerebrovascular Disease

with anaesthesia *per se* and only about 10 which considered aspects related to the practice of anaesthesia. Moreover, there were surprisingly few anaesthetists or members of anaesthetic departments among the participants. A rough count would suggest that there were not more than 23 (5% of total participants) of whom only four were from outside North America.

The present Symposium was notable also for the inauguration of the International Society of Cerebral Blood Flow and Metabolism and the launching of its official journal—*Journal of Cerebral Blood Flow and Metabolism.* The application of established techniques to measurements in acute clinical practice, the development of new techniques related particularly to cerebral metabolism and flow–metabolism coupling, and the establishment of a multidisciplinary Society are opportunities which should be grasped by anaesthetists particularly since anaesthesia is the ideal example of reversible (it is hoped) dysfunction of the brain.

William Fitch

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PLASMA CONCENTRATION OF MORPHINE AFTER I.M., EXTRADURAL AND INTRATHECAL ADMINISTRATION

M. CHAUVIN, K. SAMII, J. M. SCHERMANN, P. SANDOUK, R. BOURDON AND P. VIARS

SUMMARY

Seventeen patients received morphine 0.2 mg kg^{-1} in a 10% dextrose solution i.m. ($n = 5$), extradurally ($n = 6$) and intrathecally ($n = 6$) for pain after operation. Morphine was measured in plasma by radioimmunoassay. Plasma immunoreactive morphine concentration was significantly less after intrathecal administration than after i.m. and extradural administration ($P < 0.05$) at 2, 10, 15 and 30 min. We conclude that morphine given extradurally has a greater initial rate of vascular absorption than morphine given intrathecally and is similar to that observed after i.m. administration.

Recent reports have demonstrated that morphine injected intrathecally (Samii et al., 1979; Wang, Nauss and Thomas, 1979) and extradurally (Behar et al., 1979; Magora et al., 1980) produces a potent and prolonged analgesia which is probably caused by a direct action on spinal opiate receptors (Yaksh and Rudy, 1976; Snyder, 1977). Although plasma morphine concentrations after parenteral administration have been studied before (Spector and Vessel, 1972; Berkowitz, 1976), vascular absorption of morphine given intrathecally or extradurally has not been determined. The purpose of this study was to measure plasma morphine concentrations after i.m., extradural and intrathecal administration of the same dose of morphine.

METHODS

Seventeen patients with severe pain following laparotomy were studied. All gave informed consent. The patients were randomly allocated to three groups: morphine hydrochloride in a 10% dextrose solution was administred i.m. ($n = 5$), extradurally ($n = 6$) and intrathecally ($n = 6$). The volume of the solution injected was always less than 2 ml. The patients in the intrathecal group were maintained in a 40° head-up position and kept in the recovery room during the study. Plasma concentrations were measured by radioimmunoassay using goat antiserum (Spector and Vessel, 1972; Berkowitz, 1976) before and 2, 10, 15, 30 min, 1, 2, 3, 4, 5, 6, 9, 12 h (i.m. group), 24, 36 (extradural group) and 48 h (intrathecal group) after morphine injection. Data were expressed as mean ± SEM and statistical analyses were performed using Student's *t* test.

RESULTS

After intrathecal administration of morphine, plasma concentrations were significantly less ($P < 0.05$) than after either i.m. or extradural administration at 2 (2 ± 1, 21 ± 7 and 26 ± 9 ng ml^{-1}), 10 (14 ± 7, 51 ± 4 and 40 ± 7 ng ml^{-1}), 15 (20 ± 6, 54 ± 4 and 45 ± 8 ng ml^{-1}) and 30 min (32 ± 5, 62 ± 4 and 50 ± 6 ng ml^{-1}) (fig 1). One hour after administration, plasma concentration of morphine was still significantly less in the intrathecal group than in the i.m. group (42 ± 3 and 67 ± 6 ng ml^{-1}; $P < 0.05$). Plasma concentrations of morphine in the i.m. group were greater than in the extradural group from 10 min to 12 h. However, this difference was not statistically significant. At 36 h the plasma concentration of morphine remained increased (35 ng ml^{-1}) in one patient in the extradural group and three patients in the intrathecal group, and was reduced ($\leqslant 2$ ng ml^{-1}) in all other patients in these groups.

DISCUSSION

Our results show that initial vascular absorption rate of morphine is slower after intrathecal

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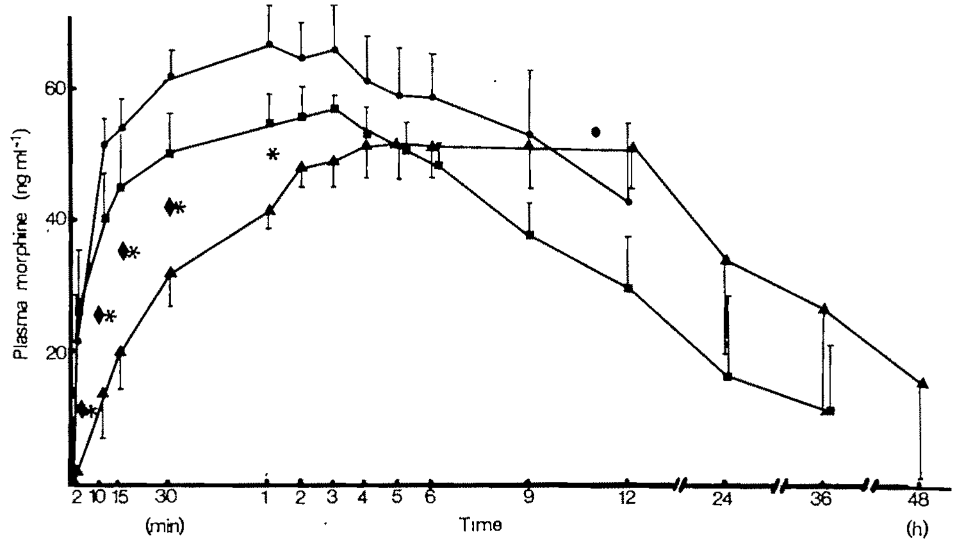

FIG. 1. Plasma immunoreactive morphine after i.m. (●) extradural (■) and intrathecal (▲) administration of morphine 0.2 mg kg^{-1} (mean ± SEM). *$P<0.05$ i.m. *v.* intrathecal groups; ◆ $P<0.05$ extradural *v.* intrathecal groups.

administration than after either i.m. or extradural injections which had a similar rate of vascular absorption.

The dose used for all patients (0.2 mg kg^{-1}) is standard for i.m. administration, but greater than doses which have been recommended for intrathecal or extradural administration. Indeed, it has been demonstrated that morphine 0.5–1 mg given intrathecally (Wang, Nauss, and Thomas, 1979) and morphine 2–3 mg given extradurally (Behar et al., 1979; Magora et al., 1980) are sufficient to produce potent analgesia without central depression. Our initial experience with larger doses of morphine given intrathecally (Samii et al., 1979) showed that respiratory depression is unusual if the patients are maintained in a head-up position after injection of a dextrose hyperbaric solution of morphine. We therefore used a similar dose of morphine (0.2 mg kg^{-1}) in the three groups of patients in order to compare rates of vascular absorption.

Our method of morphine measurement detected both unmetabolized morphine and morphine glucuronide which is the major inactive metabolite. It has been demonstrated that, after i.m. administration of morphine, morphine glucuronide concentration increases rapidly and 2 h after injection is greater than the unmetabolized morphine concentration (Berkowitz, 1976). Thus, we are able to interpret the increased plasma morphine concentrations we observed in some patients several hours after morphine administration. However, the observation of a reduced plasma morphine concentration with potent analgesia in some patients in the extradural and intrathecal groups 12–36 h after morphine administration suggests a direct action of morphine on local opiate receptors in the spinal cord. However, our method permitted us to consider the plasma morphine concentration during the first 30 min as largely composed of unmetabolized morphine. Thus, the difference in the rate of initial vascular absorption from 2 to 30 min between the intrathecal and extradural groups is meaningful. Such a difference has been already observed after intrathecal and extradural administration of lignocaine (Giasi, d'Agostino, and Covino, 1979) and is probably caused by anatomical vascular differences. Morphine applied intrathecally must diffuse from the cerebrospinal fluid into the spinal cord to be absorbed into capillaries; extradural administration will probably produce rapid absorption of some morphine by the venous plexus in the extradural space, while the remainder diffuses across the dura into the cerebrospinal fluid (Cousins et al., 1979). Extradural morphine has been reported to produce analgesia within 5 min (Behar et al., 1979; Magora et al., 1980) which is faster than after intrathecal morphine (Samii et al., 1979) and may be partly caused by rapid vascular absorption of morphine given extradurally. Subsequent diffusion from the extradural space across the dura towards the spinal opiate receptors produces prolonged spinal analgesia.

We conclude than morphine given extradurally has a higher rate of vascular absorption than morphine given intrathecally and is similar to that observed after i.m. administration.

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CONCENTRATION DE MORPHINE DANS LE PLASMA APRES ADMINISTRATION PAR VOIES INTRAMUSCULAIRE, EXTRADURALE ET INTRATHECALE

RESUME

On a administré à dix-sept patients, $0,2\,mg\,kg^{-1}$ de morphine dans une solution de dextrose à 10%: par voie intramusculaire ($n = 5$), extraduralement ($n = 6$) et intrathécalement ($n = 6$), pour soulager les douleurs après une opération. La morphine se trouvant dans le plasma a été mesurée par radio-immunologie. La concentration de morphine immunoréactive dans le plasma a été nettement moindre après l'administration intrathécale qu'après l'administration par les voies intramusculaire et extradurale ($P < 0,05$) à 2, 10, 15 et 30 min. Nous en concluons que la morphine administrée par voie extradurale a un taux initial d'absorption vasculaire plus fort que la morphine administrée par voie intrathécale, et que ce taux est similaire à celui observé après l'administration intramusculaire.

PLASMAKONZENTRATIONEN VON MORPHIUM NACH INTRAMUSKULÄRER, EXTRADURALER UND INTRATHEKALER VERABREICHUNG

ZUSAMMENFASSUNG

Seibzehn Patienten erhielten Morphium $0,2\,mg\,kg^{-1}$ in einer 10%igen Dextroselösung intramuskulär ($n = 5$), extradural ($n = 6$) und intrathekal ($n = 6$) zur postoperativen Schmerzlinderung. Das Morphium wurde im Plasma mittels Radioimmunotest gemessen. Immunoreaktive Morphiumkonzentrationen im Plasma waren nach 2, 10, 15 und 30 Minuten nach intrathekaler Verabreichung wesentlich geringer als bei den anderen Verabreichungsformen ($P < 0,05$). Daraus schliessen wir, dass extradural verabreichtes Morphium eine grössere anfängliche Gefassabsorptionsrate zeigt als bei intrathekaler Verabreichung, und ähnlich der Absorptionsrate ist, die bei intramuskulärer Verabreichung beobachtet wurde.

CONCENTRACION DE MORFINA EN EL PLASMA DESPUES DE LA ADMINISTRACION INTRAMUSCULAR, EXTRADURAL E INTRATECAL

SUMARIO

Se administró a 17 pacientes $0,2\,mg\,kg^{-1}$ de morfina en una solución de dextrosa al 10%, intramuscularmente ($n = 5$), extraduralmente ($n = 6$) e intratecalmente ($n = 6$) para aliviar el dolor posoperativo. La cantidad de morfina en el plasma se midió mediante una evaluación radioinmunológica. La concentracion de morfina inmunoreactiva en el plasma fue significativamente inferior después de la administración intratecal que las presentadas después de la administraciones intramuscular e extradural ($P < 0,05$) a intervalos de 2, 10, 15 y 30 minutos. Concluimos, por lo tanto, que la morfina administrada extraduralmente presenta un régimen inicial de absorción vascular que ès superior al de la morfina administrada intratecalmente y que es similar al observado después de la administración intramuscular.

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EXTRADURAL OPIOIDS FOR POSTOPERATIVE ANALGESIA

A double-blind comparison of pethidine, fentanyl and morphine

D. V. RUTTER, D. G. SKEWES AND M. MORGAN

SUMMARY

Pethidine 50 mg, fentanyl 100 µg and morphine 2 mg administered to the extradural space, were compared in the treatment of pain following surgery. All three drugs produced a rapid decrease in pain scores as assessed using a visual linear analogue, morphine being the least effective. Fentanyl had a relatively short duration of action (2 h), whereas morphine appeared to be the longest acting. It is suggested that the best relief of pain would be obtained by incremental doses given extradurally. All drugs produced an increase in sedation, but there was no respiratory depression as assessed by Pa_{CO_2} measurement.

Following its initial use in patients with chronic pain (Behar et al., 1979), increasing use has been made of extradural morphine in patients suffering from pain after surgery (Cousins et al., 1979; Torda, 1979; Bailey and Smith, 1980; Bromage, Camporesi and Chestnut, 1980; Graham, King and McCaughey, 1980; Magora et al., 1980; Reiz and Westberg, 1980; Wolfe and Davies, 1980). Although these authors reported excellent analgesia of long duration with minimal side-effects, others have found extradural morphine disappointing in the treatment of postoperative pain. McClure and colleagues (1980) showed no difference between the pain relief produced by morphine and a placebo 20 min after administration.

Initial experience with the technique in this department was obtained in the management of pain in patients following major hepato–biliary surgery. In eight patients, pethidine 100 mg in normal saline 10 ml was injected via an extradural catheter inserted in the mid-thoracic region. Although analgesia followed rapidly, all patients became heavily sedated, two being unrousable, and there was a marked decrease in respiratory rate, although apnoea did not occur. Significant analgesia in these patients lasted from 3 to 6 h, as assessed using a visual linear analogue scale.

Since these experiences with extradural pethidine differed from work already published it was decided to institute a double-blind study of the effectiveness of three opioid drugs: pethidine, fentanyl and morphine, in patients with pain after surgery.

PATIENTS AND METHODS

Studies were carried out on 60 patients (33 male and 27 female) in whom extradural catheters had been inserted after the induction of anaesthesia. The catheters were introduced into the mid-thoracic region for upper abdominal surgery and the lower thoracic or lumbar region for lower abdominal operations. Informed consent was obtained from each patient. Premedication was with appropriate doses of papaveretum and hyoscine and the anaesthetic consisted of an i.v. induction followed by the administration of a competitive neuromuscular blocking drug, tracheal intubation and ventilation of the lungs with 70% nitrous oxide in oxygen. Small amounts of halothane or enflurane were added to deepen anaesthesia if necessary, but i.v. analgesic drugs were not given. Following antagonism of the neuromuscular blockade at the end of the procedure, the patients were transferred to the recovery room or intensive care unit where the studies were carried out.

Pain was assessed using a visual linear analogue scale as first described by Bond and Pilowsky (1966). The patient placed a mark on the line corresponding to the degree of pain experienced and the distance (in millimetres) from the left hand edge of the line to the mark was taken as the pain score. The method was explained to each patient on the day before surgery, and anyone unable to understand was not included in the trial. Pain was assessed before the administration of the drug at

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the patient's first request for analgesia, at 5, 10, 20, 30 and 60 min after administration and at hourly intervals thereafter. Any patient who requested additional analgesia received it immediately in the form of i.m. or i.v. papaveretum and thereafter was excluded from analysis of the results.

At each assessment heart rate, arterial pressure and respiratory rate were recorded. In 38 patients (12 each in the morphine and fentanyl groups and 14 who had received pethidine) an arterial cannula had been inserted for monitoring purposes during surgery, and in these patients samples of arterial blood were taken for measurement of Pa_{CO_2}. An attempt was made to assess the degree of sedation scored: 0 = awake and alert; 1 = awake but drowsy; 2 = drowsy but rousable; 3 = unrousable.

The drugs, which were free of preservative, were prepared in the hospital pharmacy in identical coded ampoules. They contained pethidine 50 mg, fentanyl 100 µg or morphine 2 mg, all in normal saline 10 ml. They were administered in a random fashion such that 20 patients received each drug. The dose of pethidine was chosen in the light of our initial experience with the drug. The doses of morphine and fentanyl were chosen on the basis of those commonly reported by other authors (Wolfe and Nicholas, 1979; Chayen, Rudich and Borrine, 1980; McClure et al., 1980; McQuay et al., 1980). It was considered unethical to incorporate a placebo when the time of onset of analgesia was uncertain.

RESULTS

The operations performed, the number of patients who received each drug in the operative groups and their mean ages and weights are shown in table I. One patient, following herniorrhaphy, was extremely restless and voluble in the recovery room and unable to record the amount of pain experienced. He was given an analgesic solution, which was later shown to be morphine, and although he became calmer and apparently had relief of pain, was still unable to co-operate and was excluded from the trial. All remaining patients were able to co-operate with the method of assessment of pain.

The mean pain scores at each assessment are shown in table II. There was no significant difference between the pain scores in the control period. Following injection of the opioid drug there was a prompt and significant decrease in the pain scores in each group, the maximum decrease being achieved within 20–30 min. The mean pain scores in the pethidine group were significantly less than in those given morphine at 10, 20, 30 and 60 min ($P<0.05$, 0.01, 0.01 and 0.05 respectively; Student's t test), while in the fentanyl group the score was significantly less than in the morphine group at 30 min ($P<0.05$). Ten patients who had received pethidine, nine given fentanyl and four given morphine recorded zero pain score at some stage during the study. These were all recorded within 1 h of the administration of the drug, but only lasted for a maximum of 30 min in the fentanyl group and 20 min in the morphine group. Total

TABLE I. *Operations performed and number of patients receiving different analgesic agents*

	Analgesic			
Operations performed	Pethidine	Fentanyl	Morphine	Total
Upper abdominal				
Hepato-biliary	7	6	5	18
Gastric	1	4	2	7
Small bowel	2	1	1	4
Vascular	—	1	1	2
Adrenalectomy	1	—	1	2
Lower abdominal				
Gynaecological	2	3	1	6
Colectomy	2	1	3	6
Vascular	3	1	2	6
Herniorrhaphy	2	3	3	8
Total				59
Mean age ± SEM (yr)	52.6 ± 3.12	46.4 ± 3.0	51.0 ± 3.4	
Mean weight ± SEM (kg)	64.2 ± 3.2	68.2 ± 3.0	64.4 ± 2.9	

TABLE II. *Mean pain scores ± SEM at each assessment and number of patients at each time*

Time	Pain scores ± SEM Pethidine	*n*	Fentanyl	*n*	Morphine	*n*
Control	66.7±3.91	20	67.4±4.39	20	68.2±4.82	19
5 min	37.9±5.81	20	32.1±4.40	20	40.9±6.39	19
10 min	13.8±4.57	20	22.5±3.88	20	28.3±5.09	19
20 min	7.9±3.42	20	16.6±4.40	20	26.2±4.31	19
30 min	10.1±3.74	20	13.7±3.83	20	24.4±3.48	19
1 h	11.9±3.89	20	21.6±4.44	20	24.1±3.70	19
2 h	23.1±4.31	20	45.9±5.75	19	35.3±4.98	18
3 h	35.5±5.15	19	49.5±5.10	12	34.8±6.45	15
4 h	42.1±5.89	14	51.6±10.59	5	37.8±8.69	12
5 h	40.1±7.75	9			38.8±8.84	9
6 h	39.8±16.05	4			17.6±5.23	5

analgesia occurred for a significant time in only two patients, both given pethidine (2 h and 5 h respectively).

By 2 h there was an increase in pain score in all groups, being most marked in those given fentanyl, and at this time the mean pain score in these patients was significantly greater than in those who received pethidine. By 4 h, 15 of the fentanyl group had been withdrawn from the study as they had received further analgesia. There was little increase in pain scores in the morphine group after 2 h and only a small increase in those who had received pethidine. Apart from the 4-h recording in the fentanyl group, the pain scores at each time of assessment were significantly lower than the control values for that particular group.

TABLE III. *Pattern of cumulative withdrawal of patients from the trial*

	Assessment time (h) 1	2	3	4	5	6	7
Morphine (19)	0	1	4	7	10	14	14
Pethidine (20)	0	0	1	6	11	16	19
Fentanyl (20)	0	1	8	15	17	18	20

TABLE IV. *Number of patients whose pain scores were 50% or less of control values at each assessment time*

	Time (min) 5	10	20	30	60	(h) 2	3	4	5	6	7
Morphine (19)	7	11	10	15	14	10	7	6	7	5	3
Pethidine (20)	8	16	18	17	17	14	8	4	2	2	1
Fentanyl (20)	9	16	19	19	16	8	3	2	2	2	0

The results are complicated by the fact that patients were withdrawn progressively from the trial as they required additional analgesia, so that the mean pain scores alone could be misleading. Table III shows the pattern of the withdrawal of patients in a cumulative fashion. At 3 h, significantly more patients who had been given fentanyl than had received pethidine had been withdrawn ($P < 0.01$, Fisher's exact test), but the difference between morphine and fentanyl did not quite reach statistical significance. By 4 h, the majority of patients in the fentanyl group had been withdrawn, the number remaining in the other groups being significantly greater. By 7 h, more of the patients who had received pethidine and been withdrawn compared with the morphine group, although the difference was not statistically significant. Table IV shows the number of patients at each time of assessment in whom the pain scores were 50% or less of the control values. These results, taken with the pattern of withdrawal, indicate that fentanyl had a relatively short duration of action when given to the extradural space whereas, of the three agents, morphine produced the longest effect.

The changes in respiratory rate, Pa_{CO_2} and degree of sedation are shown in figure 1. There was a decrease in respiratory rate following each drug, being least with morphine, but it was significantly less than control values from 5 min to 2 h in the

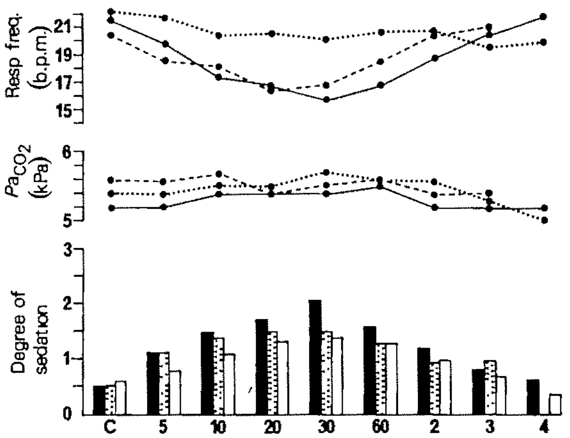

FIG. 1. Respiratory frequency (b.p.m.), Pa_{CO_2} (kPa) and degree of sedation. Black columns, ●——● = pethidine; dotted columns, ●- - -● = fentanyl; open columns, ●...● = morphine.

pethidine group, and at 20 min in those given fentanyl. There were no significant changes in Pa_{O_2}. An increase in sedation was immediately obvious, being maximum at 30 min with each drug, and persisting for 3 h. At no stage did any patient become unrousable or give cause for concern.

No significant changes occurred in heart rate or arterial pressure during the study, and no patient complained of nausea, vomiting or itching. No sensory or motor loss was detected at any stage.

DISCUSSION

All three drugs used in this study produced a rapid and significant decrease in pain scores when injected into the extradural space. However, the duration of action differed from that reported by other workers in that it was much shorter. The pain scores alone cannot be the only factor to be taken into account when looking at the duration of action because of the progressive withdrawal of patients from the study as they required additional analgesia. When looked at in this way, fentanyl appeared to produce satisfactory analgesia for about 2 h, while morphine appeared to have the longest duration of action.

Doubt must be raised as to the reliability of taking the duration of action of an analgesic drug, in these circumstances, as the time to the next administration of a narcotic agent. This cannot be equated with the time by which further relief of pain is required. The administration of additional analgesia depends on the patient requesting further medication and on the availability of a trained nurse. Cousins and colleagues (1979) measured pain relief using a visual linear analogue scale and found that the mean duration of action of pethidine 100 mg, given extradurally for the relief of pain after operation, was 6 h. McClure and co-workers (1980), using a similar method of assessment, found extradural morphine 2 mg and 5 mg to be disappointing in the treatment of pain following surgery and to be ineffective when used immediately after operation.

No complications were seen that could be attributed to the extradural opioids, and the frequency of complications following extradural morphine would seem to be lower than by conventional routes of administration (Reiz and Westberg, 1980). The most serious side-effect was respiratory depression. In all our patients there was a decrease in respiratory rate, but this was never a problem and there was no depression of ventilation, as judged by change in Pa_{CO_2}. However, there has been a number of reports of severe respiratory depression and coma following the use of extradural opioids, although the timing of the depression appears to vary. In most instances it occurred within 45 min of administration (Glynn et al., 1979; Scott and McClure, 1979; Boas, 1980; Welch, 1981), although in some it was delayed for 4–6 h (Christensen, 1980; Reiz and Westberg, 1980). Glynn and colleagues (1979) showed that the respiratory depression coincided with high c.s.f. concentrations of pethidine and suggested that this, combined with the effects of the narcotic premedication given some time earlier, could be the cause. This early occurrence of respiratory depression after extradural administration is in marked contrast to that seen after intrathecal opioids, where several hours often elapse before any serious effects are seen (Glynn et al., 1979; Lolios and Andersen, 1979; Davies, Tolhurst-Cleaver and James, 1980). Glynn and co-workers (1979) have commented on the fact that there is virtually no information on the rate of removal of drugs from c.s.f. and that many factors such as changes in posture, coughing and vascular pulsations would affect c.s.f. flow and hence the movement of any contained narcotics.

Systemic absorption of extradural opioids is unlikely to be a major factor in the production of analgesia. Yaksh and Rudy (1976) produced potent analgesia in rats with intrathecal morphine and showed that the latter was confined to the spinal cord. Cousins and colleagues (1979) measured blood and c.s.f. concentrations of pethidine after extradural administration and found that the onset of pain relief coincided with high c.s.f. concentrations while the blood pethidine concentrations were below the analgesic value. However, systemic effects do occur, as indicated by the increase in sedation observed following all three drugs and which was maximum at 30 min. Bromage, Camporesi and Chestnut (1980) found less central depression following extradural opioids than after approximately the same dose of opiate i.v.

There is considerable enthusiasm for the use of extradural opioids in the treatment of all types of pain. There is no doubt that they produce rapid relief of pain, but the duration of action found here was much shorter than that reported by others. This may be related to the method of assessment of the pain. It is also interesting to note that Husemeyer, O'Connor and Davenport (1980) found extradural morphine to be ineffective in relieving pain in labour. Of the drugs used in this study, pethidine appeared to be the most effective and morphine the least, but this is probably a matter of dosage. More effective analgesia could probably have been obtained with morphine by titrating the extradural dose against the demands of the patients (Bromage, Camporesi and Chestnut, 1980). The duration of action of fentanyl was relatively short and a continuous infusion, with which excellent results have been reported (Bailey and Smith, 1980), would be more appropriate.

Serious side-effects do occur at a variable time after the administration of extradural opioids, and they are potentially lethal. Little is known of the factors that contribute to the appearance of severe respiratory depression. Despite the many advantages that this technique appears to offer, more work needs to be done to elucidate these factors and at the moment the authors are not prepared to use extradural opioids for analgesia after surgery unless the patient is under constant expert surveillance.

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OPIACES PAR VOIE EXTRADURALE POUR ANALGESIE POSTOPERATOIRE: COMPARAISON Á DOUBLE INCONNUE DE LA PÉTHIDINE, DU FENTANYL ET DE LA MORPHINE

RESUMÉ

On a comparé 50 mg de péthidine, 100 µg de fentanyl et 2 mg de morphine administrés dans l'espace extradural, pour le traitement de la douleur faisant suite à une intervention chirurgicale. Ces trois agents ont entraîné une rapide diminution de la douleur, estimée à l'aide d'un analogue linéaire visuel, la morphine étant le produit le moins efficace. Le fentanyl a eu une durée d'action relativement courte (2 h), alors que la morphine semble avoir été l'agent ayant la plus longue durée d'action. L'auteur est d'avis qu'un meilleur soulagement de la douleur pourrait être obtenu par des doses croissantes administrées par voie extradurale. Tous les produits ont accru la sédation, mais il n'y a eu aucune dépression respiratoire comme on a pu en juger par la mesure de la Pa_{CO_2}.

EXTRADURALE OPIATE ZUR POSTOPERATIVEN ANALGESIE EIN DOPPELBLINDVERGLEICH ZWISCHEN PETHIDIN, FENTANYL UND MORPHIN

ZUSAMMENFASSUNG

Pethidin 50 mg, Fentanyl 100 µg und Morphin 2 mg, im Extraduralraum verabreicht, wurden in Bezug auf Schmerzenslinderung nach der Chirurgie verglichen. Alle drei führten zu einem raschen Rüchgang der Schmerzenswerte, die mit einer optischen linearen Analogausgabeeinheit ermittelt wurden, wobei Morphin die schwächste Wirkung zeigte. Fentanyl hatte eine relative jurze Wirkungsdauer (2 Stunden), und Morphin die längste. Es liegt nahe, dass die erfolgreichste Schmerzenslinderung durch eine gestufte extradurale Verabreichung zu erzielen ist. Alle drei führten zu einer gesteigerten Beruhigung der Patienten, aber es stellte sich keine Atmungsdepression gemessen an der Pa_{CO_2} ein.

OPIATOS EXTRADURALES PARA ANALGESIA POSOPERATIVA: UNA COMPARACIÓN DE DOBLE ANONIMATO DE LA PETIDINA, EL FENTANILO Y LA MORFINA

SUMARIO

A la cavidad extradural se le administraron 50 mg de petidina, 100 µg de fentanilo y 2 mg de morfina, cuyos efectos se compararon en el tratamiento del dolor después de la operación quirúrjica. Las tres drogas produjeron una rápida disminución de los umbrales de dolor, según evaluación efectuada mediante una analogía lineal y visual. El fentanilo presentó una actividad relativamente corta (2 h), mientras que la morfina pareció ser la más duradera. Se sugiere que el mejor alivio del dolor se obtendría incrementando las dosis administradas extraduralmente. Todas las drogas produjeron un incremento de la sedación pero no hubo depresión respiratoria según los evaluación llevada a cabo por las medición del Pa_{CO_2}.

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EXTRADURAL MORPHINE FOR PAIN AFTER SURGERY

W. A. CHAMBERS, C. J. SINCLAIR AND D. B. SCOTT

SUMMARY

The effects of 10 mg of morphine sulphate given either extradurally or i.m. for the relief of pain after operation were compared in two randomized double-blind trials in patients undergoing major gynaecological surgery. In the first trial when morphine was given with the local anaesthetic before surgery, extradural administration resulted in significantly longer lasting analgesia: mean 707 min compared with 371 min (i.m.). In the second trial in patients complaining of pain after operation, extradural morphine had a slower onset of action, but longer duration of action compared with i.m. morphine, although the differences were not statistically significant. In this group extradural morphine often failed to provide useful analgesia. The extradural group received significantly less additional morphine (6.75 mg) than did the i.m. group (18.75 mg) in the following 24 h.

In spite of numerous reports of opiates administered to the extradural space in the treatment of acute and chronic pain (Behar et al., 1979; Bromage, Camporesi and Chestnut, 1980; Chayen, Rudick and Borvine, 1980; Magora et al., 1980; Torda et al., 1980) there have been few controlled studies. In a previous report of the effects of extradural saline 10 ml, either alone or with morphine sulphate 2 or 5 mg added, in 30 patients studied on the day after major gynaecological surgery involving laparotomy (McClure et al., 1980) there was no difference between the groups with regard to the mean reduction in pain score at 20 min after injection. Although the patients who had received the placebo required analgesia sooner than those who had received morphine, this would have occurred regardless of its route of administration. We conducted the following studies to compare the effects of morphine sulphate 10 mg administered either extradurally or i.m. One study involved morphine injections before the occurrence of pain (just before surgery) and the other 24 h after operation when pain was present. In this way it was hoped to assess the efficacy of extradural morphine both in preventing and in treating pain after operation.

METHODS

Two studies, each involving two groups of 10 patients had the approval of the local ethics committee. The patients were about to undergo major gynaecological surgery involving laparotomy and informed consent was obtained.

Study I

Premedication was diazepam 10 mg orally and atropine 0.6 mg i.m. 1 h before anaesthesia.

Extradural block was performed using a catheter inserted through L1/T12 interspace. Injection of 20 ml of 0.5% bupivacaine was made with the patient lying supine and, 2–3 min later, general anaesthesia was induced with thiopentone 500 mg and maintained with 0.5% halothane in 66% nitrous oxide in oxygen from a circle system using a face-mask. Operating conditions were entirely satisfactory in all cases. Bupivacaine was chosen as we wished to have the patients awake and co-operative before the onset of pain after operation.

Morphine 10 mg was given to all patients either by adding it to the bupivacaine (10 patients) or by i.m. injection (10). Because i.m. morphine is sometimes painful, it was not given until immediately after thiopentone administration. Those given morphine extradurally were given an i.m. injection of saline immediately after the thiopentone. The person administrating the morphine did so by reference to a randomized list just before the extradural injection was given. He took no part in the assessment of pain after operation.

Assessment of pain after operation. All patients were seen 2.5, 3, 4, 6 and 8 h after the extradural injection by the same nurse observer who was unaware of the route of administration of the morphine and had not been present in the anaesthetic or operating room. The patients were asked

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to assess their pain on a visual analogue scale—an unmarked 10-cm line the opposite ends of which were labelled NO PAIN and SEVERE PAIN—which had been explained to them before the operation. Heart rate, arterial pressure and respiratory rate were recorded together with the upper dermatomal level (as judged by loss of pinprick) of the remaining extradural blockade. Analgesics were given by the nursing staff using their normal clinical criteria.

Study II

In this study all observations on pain were made on the day after operation. In view of this, the routine practice was used in premedication and in the local anaesthetic agents used.

Premedication consisted of diamorphine 5 mg and atropine 0.6 mg given 1 h before operation.

Extradural block was obtained by injecting 20 ml of 2% lignocaine via a catheter. This was followed by light general anaesthesia as in study I.

Pain relief after operation was obtained in most cases with a continuous extradural infusion of 0.25% bupivacaine 8–10 ml h^{-1}. However, this method was not available on four occasions (two patients in each group). These patients received a single injection of morphine 5 mg in 10 ml of normal saline extradurally when they required analgesia on the day of operation. The bupivacaine infusions were stopped at 6 a.m. on the following day and patients were accepted into the trial if and when they required further analgesia during the morning.

Assessment of pain was made using a visual analogue scale. Two injections were then given, one i.m. and one extradural, the patients being told that they were receiving a pain-killing drug. In one group of 10 patients morphine 10 mg was given extradurally in 10 ml of saline, together with an i.m. injection of 1 ml of saline. The other 10 patients received morphine 10 mg i.m. and 10 ml of saline extradurally. Thus all patients received 10 mg of morphine, 10 extradurally and the other 10 i.m. The order was randomized and the person making up the two injections for each patient took no part in assessing the effects.

Analogue scale assessments were made at 20, 40, 60, 120, 240, 360 and 480 min after the morphine administration, provided no further analgesia had been given. The ward staff were free to give opiate analgesics at any time and if this was done the study was terminated at that point.

The results were assessed using either the Student's *t* test or Wilcoxon's rank sum test as appropriate, $P < 0.05$ being taken to indicate a significant difference.

RESULTS

The mean age of the 40 patients was 38.1 yr, the mean weight 61 kg and the mean height 160 cm. The mean duration of surgery was 110 min. There were no statistically significant differences between the different groups of patients with regard to these variables.

Study I

While the local anaesthetic effect of bupivacaine was still effective, all pain scores were low. There was no obvious difference between the two groups with regard to duration of spinal nerve block, regression to T12 occurring after about 6 h. All the patients who had received i.m. morphine required analgesia as the sensory block regressed below T12. In contrast only three of those who had received extradural morphine required analgesia at this time and the other seven remained comfortable. The mean time to the first administration of analgesia after the preoperative injection was 371 ± SEM 25.9 min in the i.m. group compared with 707 ± 92.5 min in the extradural group. This difference was highly significant ($P < 0.01$). Individual times are shown in figure 1.

One patient in each group received cyclizine because of nausea. Three patients who had received extradural morphine complained of an itchy face, although this was not particularly troublesome, and two of these were those who obtained the longest duration of pain relief. One patient who had received extradural morphine had a delayed recovery from anaesthesia and 30 min after surgery had been completed, she had not regained consciousness. She had pin-point pupils and her respiratory rate was 10 b.p.m. Following the administration of naloxone 0.2 mg i.v. she regained consciousness and was free of pain. She had no further episodes of depression of consciousness or respiration over the ensuing 24 h.

Study II

No patient required further analgesia before 1 h. The mean pain scores up to that time are shown in figure 2. There was no significant difference between the mean pain scores before injection and, although the patients in the i.m. group tended to

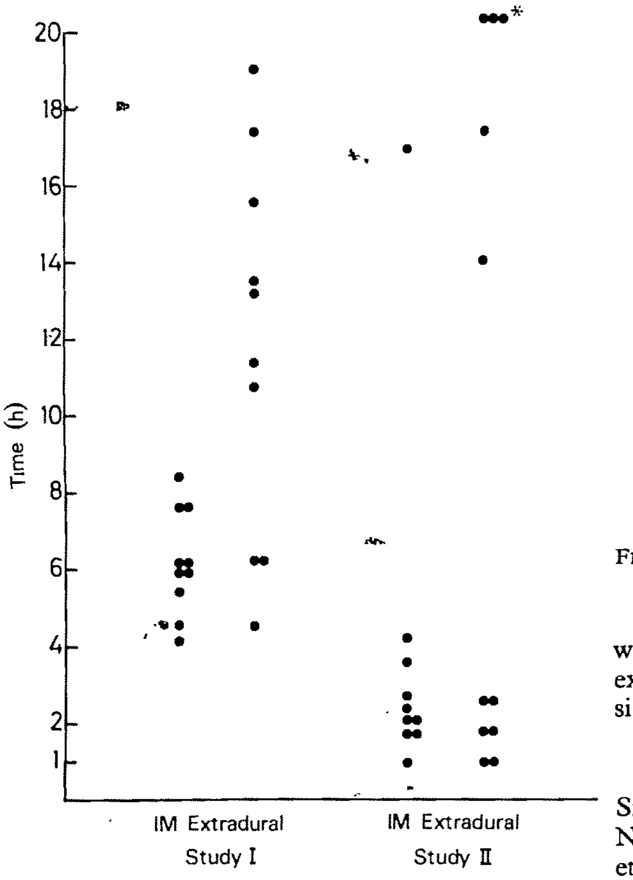

FIG. 1. Times (h) from extradural and i.m. injection until next administration of analgesic in patients who had received morphine extradurally and others who had received morphine i.m. in the two studies. * Three patients in study II required no further analgesic.

have a greater reduction in pain score at 1 h, this was not statistically significant (table I, fig. 2). Three patients who had received extradural morphine did not receive any further analgesia, but the difference between the groups was not statistically significant. The actual times to further analgesia are shown in figure 1, alongside those from study I. The mean total dose of morphine given over the 24 h following the extradural and i.m. injections

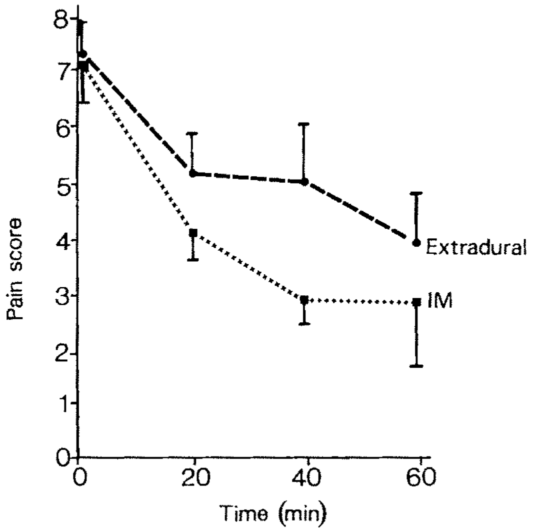

FIG. 2. Mean pain scores in patients in study II who had received morphine 10 mg by i.m. or extradural injection.

was 18.7 mg in the i.m. group and 6.7 mg in the extradural group; this difference was statistically significant.

DISCUSSION

Since the first descriptions of intrathecal (Wang, Nauss and Thomas, 1979) and extradural (Behar, et al., 1979) morphine for pain relief, many reports have been published and the great majority have been favourable. However, few properly controlled studies have been carried out and quite frequently it is not possible to determine if the opiate gave analgesia as a direct effect on the spinal cord or by a central effect following systemic absorption.

There has been a trend also towards larger and larger dosage, particularly with extradural administration, presumably because the small doses originally recommended were found to be ineffective. Thus the 2 mg of morphine first described by Behar is now seldom used and 10 mg appears to be the dose most commonly used.

TABLE I. *Patients in study II: Mean (± SEM) pain scores before injection and at 20, 40 and 60 min after injection in the two groups of patients*

	Before injection	20 min	40 min	60 min
I.m.	7.10±0.68	4.15±0.54	2.85±0.47	2.80±1.40
Extradural	7.25±0.61	5.15±0.75	4.90±1.06	3.85±0.92

In a previous controlled study (McClure et al., 1980) morphine 2 mg and 5 mg given extradurally were compared with a placebo injection in patients suffering from postoperative pain similar to those in the present two studies. It was found that 5 mg gave better results than 2 mg, which itself was better than placebo. However, the same result might have been obtained with i.m. injection. Both doses of morphine frequently failed to provide any significant or long-lasting analgesia. Placebo reactors were also common, one patient requiring no pain relief for 8 h after the injection of saline. At 20 min after injection, the placebo group as a whole had a statistically significant reduction in the mean pain score.

In the present studies we were impressed by the much better results we obtained in regard to pain relief when the morphine was given before the onset of pain—in study I when mixed with the local anaesthetic drug before operation. In seven of 10 patients it took from 11 to 19 h before further analgesia was required. This compares with a mean of 6 h for those given morphine 10 mg i.m. just before operation, a figure we found surprisingly large and probably because of the long duration of analgesia found with a dose of 20 ml of 0.5% bupivacaine.

If pain was present before giving morphine, as was the case in study II, the results, although still favouring the extradural route, were less impressive. Minor and short-lived analgesia occurred in four of 10 patients in the extradural group. Indeed, the degree of analgesia during the 1st hour was better in the i.m. group. The impression gained was that extradural morphine frequently failed in the patient with pain because the onset of analgesia was so prolonged. This statement must be contrasted with the frequent reports that analgesia (almost always total) appears within a few minutes, lasts many hours and all this in 100% of patients. Such assertions are both unrealistic and liable to bring the method into disrepute.

The exact mechanism by which intraspinal opiates work is not clear, although the theoretical reasons why it should mimic naturally occurring endorphins are cogent. That this explanation does not meet all aspects of the problem is also becoming clear. Pain is a multifactorial phenomenon and the pain of labour, for example, cannot be compared to chronic pain or even the acute pain of the period after operation. Clinically it has been shown that the relief of labour pain using small (2-mg) doses of morphine extradurally is almost totally useless and the dose must be increased to that commonly used for i.m. injection (10 mg). This also holds for other drugs such as fentanyl, of which, in one study reporting favourably (Nalda, Camp and Burzaco, 1981), a mean dose of 0.25 mg was used. As the dose of opiate is increased there can be no doubt that a substantial part of the effect will be attributable to systemic absorption, the extradural space presenting little in the way of a barrier to this process.

As experience with intraspinal opiates increases so do the number of reported side-effects. These include respiratory depression, nausea and vomiting, intractable pruritis and coma. Subarachnoid injection seems to be particularly liable to cause respiratory depression, but extradural injection also does so on occasion. One of our patients receiving extradural morphine before operation could not be roused after operation until naloxone had been given.

The present practice of intraspinal opiate administration requires elucidation and this can only be realized with properly controlled studies. Thus, we need data on the degree and duration of analgesia compared with the more usual routes of administration, the effect of dosage and, above all, the nature and frequency of side-effects.

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MORPHINE ADMINISTREE PAR VOIE EXTRADURALE POUR LE SOULAGEMENT DE LA DOULEUR APRES UNE INTERVENTION CHIRURGICALE

RESUME

Nous avons comparé, au cours d'études à double inconnue effectuées au hasard, les effets de 10 mg de sulfate de morphine administrés soit par voie extradurale, soit par voie intramusculaire afin de soulager les douleurs postopératoires ressenties par des patientes ayant subi des opérations gynécologiques majeures. Au cours de la première étude, la morphine a été administrée en même temps que l'agent anesthésiant local avant l'intervention, et l'administration extradurale a eu pour effet de produire une analgésie d'une durée nettemment plus longue: moyenne 707 min contre 371 min avec l'injection intramusculaire. Lors de la seconde étude, effectuée sur des patientes se plaignant de douleurs postopératoires, la morphine administrée par voie extradurale a demandé plus de temps avant d'agir, mais sa durée d'action a été plus longue qu'avec l'administration de morphine par voie intramusculaire, bien que les écarts n'aient pas eu une bien grande importance statistique. Dans ce groupe, la morphine administrée par voie extradurale n'a pas toujours entraîné d'analgésie utile. Le groupe auquel la morphine avait été administrée par voie extradurale a reçu nettement moins de morphine supplémentaire (6,75 mg) au cours des 24 h suivantes que le groupe recevant la morphine par voie intramusculaire (18,75 mg).

EXTRADURALES MORPHIN ZUR SCHMERZENSLINDERUNG NACH DER CHIRURGIE

ZUSAMMENFASSUNG

Die Auswirkungen von 10 mg Morphinsulfat, entweder extradural oder intramuskulär verabreicht zur Schmerzenslinderung nach der Operation, wurden in zwei randomisierten Doppelblindversuchen mit Patienten verglichen, die sich schwerer gynäkologischer Chirurgie unterzogen. Als beim ersten Versuch Morphin zur gleichen Zeit wie die örtliche Betäubung vor der Chirurgie verabreicht wurde, führte die extradurale Verabreichung zu einer bedeutend länger anhaltenden Analgesie—im Durchschnitt 707 min im Vergleich zu 371 min bei intramuskularer Verabreichung. Beim zweiten Versuch mit Patienten, die sich nach der Operation über Schmerzen beklagten, setzte die Wirkung von extraduralem Morphin langsamer ein, hielt aber länger als bei intramuskulärem Morphin an, obwohl die Unterschiede statistisch unbedeutenden waren. Bei dieser Gruppe hatte extradurales Morphin oft keine brauchbare Wirkung. Die Gruppe von Patienten, die Morphin extradural bekamen, erhielt bedeutend weniger zusätzliches Morphin (6,75 mg) in den nachfolgenden 24 Stunden als die Gruppe, die Morphin intramuskulär bekam (18,75 mg).

MORFINA EXTRADURAL PARA EL DOLOR POSOPERATORIO

SUMARIO

Los efectos de 10 mg de sulfato de morfina, administrados extradural o intramuscularmente, para el alivio del dolor posoperatorio, se compararon en dos pruebas aleatorizadas de doble anonimato, en pacientes sometidos a operaciones quirúrjicas de importancia. En la primera preuba, en la que la morfina se administró junto con la anestesia local antes de la operación, la administración extradural tuvo como resultado una anestesia cuya duración fue significativamente mucho más large: Media de 707 min en comparación con los 371 min (intramuscular). En la segunda prueba y en pacientes aquejados de dolor posoperatorio, la morfina extradural tuvo un inicio de actividad más lento pero una actividad más duradera, en comparación con la morfina intramuscular, aunque la diferencia no era relevante desde el punto de vista estadístico. En lo tocante a este grupo, la morfina extradural no proveyó una analgesia útil. El grupo extradural recibió, de forma significativa, menos cantidad de morfina complementaria (6,75 mg) que el grupo de administración intramuscular (18,75 mg) durante las 24 horas siguientes.

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COMPARISON OF MEPTAZINOL AND PETHIDINE GIVEN I.V. ON DEMAND IN THE MANAGEMENT OF POSTOPERATIVE PAIN

P. J. SLATTERY, M. HARMER, M. ROSEN AND M. D. VICKERS

SUMMARY

Meptazinol and pethidine were compared under double-blind conditions in 20 patients, using an on-demand analgesic system to provide pain relief after upper abdominal surgery. The degree of analgesia, subjectively assessed, was good with both meptazinol and pethidine; although meptazinol produced significantly more nausea than did pethidine ($P < 0.01$), there was no statistically significant difference in the frequency of other side-effects. Over 24 h average consumption of meptazinol was 2.4 times that of pethidine, suggesting that, when given by i.v. injection, meptazinol is less potent than pethidine.

Meptazinol (m-(3-ethyl-1-methyl hexahydro-1-H-azepin-3-yl) phenol hydrochloride), an opiate antagonist, has been shown in animal studies to have potent analgesic effects and low dependence liability (Goode and White, 1971). In man, i.v. administration of meptazinol 1 mg kg^{-1} to six volunteers produced no significant changes in arterial pressure and heart rate, and gave generally satisfactory relief of pain in 39 patients suffering from renal colic (Oosterlinck and deSy, 1975). Meptazinol administered by i.m. injection to patients recovering from lower abdominal and orthopaedic surgery has been found to give good relief of pain after operation (Paymaster, 1976, 1977; Hedges, Turner and Wadsworth, 1980). In an open study in our department, meptazinol given by i.v. injection produced good relief of severe pain after operation without inducing sedation in six of eight patients. Meptazinol 100 mg i.m. causes little respiratory depression when given to conscious pain-free volunteers (Jordan et al., 1979).

Pethidine is a suitable standard for comparison: it is widely used as a postoperative analgesic, and has been successfully used in an i.v. on-demand infusion system (Chakravarty et al., 1979).

Several analgesic drugs were compared in a double-blind trial utilizing on-demand i.v. infusion to provide analgesia for patients recovering from upper abdominal surgery. We report here the results obtained for pethidine and meptazinol.

METHODS

Patients in the trial presented for elective upper abdominal surgery, had no complications and were within the age range 16–70 yr. Females who were pregnant were excluded. The trial was conducted double-blind, patients being allocated randomly to groups of 10, to receive pethidine or meptazinol for 24 h after operation. The analgesic was administered i.v. by a patient-controlled syringe pump (Evans et al., 1976), available as the Cardiff Palliator (Pye Dynamic Ltd). Each patient was visited on the evening before surgery to obtain informed consent, and was instructed in the use of the apparatus and introduced to the concept of the linear analogue (Huskisson, 1974; Revill et al., 1976).

The patients were premedicated with diazepam (approximately 0.15 mg kg^{-1}) administered orally 1–2 h before operation. Anaesthesia was induced with i.v. thiopentone, the trachea intubated after the administration of suxamethonium or a non-depolarizing muscle relaxant and the lungs were ventilated with halothane in nitrous oxide in oxygen. Up to 0.2 mg of fentanyl was given i.v. At the end of the operation residual neuromuscular blockade was antagonized using atropine and neostigmine.

On arrival in the recovery ward the Cardiff Palliator was connected to the patient's i.v. infusion using a valved Y connector (Rosen and Williams, 1979). The Palliator was set to deliver an incremental dose of 1 ml of analgesic solution with a minimum interval of 10 min between doses. The analgesic concentrations were meptazinol 50 mg ml^{-1} and pethidine 30 mg ml^{-1}—concentrations found to be appropriate in preliminary

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open studies. On wakening, the patient was given the demand control and reminded of how to use it; if necessary the patient was helped with the initial doses. Patients were kept in the recovery ward until able to use the Palliator without assistance, and then returned to the surgical ward free to take the analgesic as required. Arterial pressure, heart rate and respiratory frequency were recorded as usual by ward staff. Metoclopramide 10 mg to be given i.m. was prescribed for any patient who complained of nausea or vomited, and an alternative i.m. analgesic regime was provided in the event of rejection of the i.v. on-demand system.

Between 2 and 4 h after operation the patients were visited on the ward by a research nurse, assessed with regard to physical and conscious state, and questioned as to the degree of pain, dizziness, nausea and change of mood. At 24 h after operation, patients were again visited and asked to mark linear analogues representing overall pain, dizziness, drowsiness, nausea and mood. Patients were also questioned directly concerning pain and the occurrence of unpleasant dreams. The Palliator was then removed and an analgesic prescribed to be given i.m. when required.

Examination of the distribution of linear analogue scores for dizziness, nausea, elation and depression showed positive skew, so these scores for the two drugs were compared using the Mann–Whitney *U* test, which was also used to analyse non-continuous data. Qualitative data were analysed by the Fisher Exact Probability test.

RESULTS

The group of patients reported here consisted of 15 females and five males. By chance the meptazinol group were heavier than the pethidine group, so all drug consumptions are compared in weight-related terms. Details of each patient are presented in table I.

The number of demands made in 24 h and the quantity of drug used by each group is shown in table II.

2–4 h assessment. Observer assessment consisted of noting the presence or absence of sweating, pallor, retching or wincing. The frequency of these occurrences in the two groups was compared using the Fisher Exact Probability test and found not to be significantly different (table III).

Conscious state was assessed on a 1–4 scale and the patients were questioned regarding pain, dizziness, nausea and mood change, using a 1–5 scale for degree. These scores were compared using the Mann–Witney *U* test. Analysis of all the 2–4 h assessment scores showed no significant differences between those receiving pethidine and those receiving meptazinol.

24-h assessment. At the end of 24 h the patients were requested to mark six 10-cm linear analogues. The linear analogue for each sensation ranged from none at one end to the greatest imaginable degree at the other. The subject of each analogue and the results, given on a 0–100 scale, are shown in table IV.

Analysis of linear analogue scores by the Mann–Whitney *U* test showed that patients

TABLE I. *Patient details. *This patient was removed from the trial after 19 h because of unsatisfactory analgesia. The dose shown is that consumed in 19 h. Data from this patient are not included in further statistical analyses*

Pethidine						Meptazinol					
No.	Age (yr)	Sex	Wt (kg)	Operation	Total dose (mg)	No.	Age (yr)	Sex	Wt (kg)	Operation	Total dose (mg)
1	57	F	68	Cholecystectomy	240	1*	61	M	71	Cholecystectomy	3450
2	53	F	47	Cholecystectomy	420	2	34	F	69	Cholecystectomy	2900
3	31	F	80	Cholecystectomy	540	3	48	F	75	Cholecystectomy	2050
4	51	F	63	Cholecystectomy	390	4	45	F	67	Cholecystectomy	750
5	52	F	51	Cholecystectomy	330	5	36	F	75	Cholecystectomy	1650
6	57	F	70	Cholecystectomy	930	6	41	F	83	Cholecystectomy	1050
7	47	F	57	Cholecystectomy	840	7	46	M	89	Cholecystectomy	1050
8	59	M	56	Vagotomy	780	8	47	F	70	Cholecystectomy	2800
9	58	F	56	Cholecystectomy	690	9	49	M	85	Vagotomy	2900
10	54	F	73	Cholecystectomy	960	10	60	M	82	Cholecystectomy	1350
Mean	52		62			Mean	47		77		

TABLE II. *Analgesic doses*

	No. of demands in 24 h	Dose (mg)	Dose ($mg\,kg^{-1}$ per 24 h)
Pethidine ($n = 10$)			
Mean	19	570	9.94
Range	8–32	240–960	3.52–14.83
SD	10.0		4.04
SEM	3.2		1.28
Meptazinol ($n = 9$)			
Mean	37	1850	24.16
Range	15–58	750–2900	11.19–42.03
SD	17.2		12.20
SEM	5.7		4.07

TABLE III. *2–4 h postoperative observer assessment (number in each group with positive observation). *Assessed by Fisher's Exact Probability test*

Observations	Pethidine ($n = 10$)	Meptazinol ($n = 9$)	Significance*
Sweating	1	3	$P = 0.25$
Pallor	5	4	$P = 0.58$
Retching	1	1	$P = 0.74$
Wincing	0	2	$P = 0.21$

TABLE IV. *Linear analogue results. *0 = none; 100 = extreme. †Assessed by Mann–Whitney* U *test*

	Analogue score* (mean ± SEM)		
	Pethidine	Meptazinol	Significance†
Pain	42.7±8.7	43.1±9.2	$P > 0.05$
Drowsiness	55.3±13.5	52.2±12.6	$P > 0.05$
Dizziness	3.5±1.9	24.1±11.5	$P > 0.05$
Nausea	5.5±5.0	56.8±11.8	$P < 0.01$
Elation	25.5±9.8	27.2±13.1	$P > 0.05$
Depression	9.3±5.0	24.2±11.2	$P > 0.05$

receiving meptazinol experienced significantly more nausea than those receiving pethidine ($P < 0.01$); dizziness scores were also greater, but not significantly so.

All patients were questioned as to the overall degree of pain felt, using a five-point scale ranging from no pain to very severe pain. A similar scale was used to assess unpleasant dreaming. The dream and pain ratings were compared and there was no significant difference between the two groups in either of these ratings. Antiemetics were administered to six patients in the pethidine group, and to eight patients in the meptazinol group.

From the collected data it was possible to calculate the mean analgesic consumption for selected intervals within the 24-h period. This information is presented in table V.

TABLE V. *Time-related analgesic consumption*

Interval after operation (h)	Analgesic consumption ($mg\,kg^{-1}\,h^{-1}$) (mean ± SEM)		Relative consumption (meptazinol/pethidine)
	Pethidine	Meptazinol	
0–3	0.68±0.06	1.87±0.28	2.75 times
3–6	0.35±0.05	1.64±2.28	4.5 times
6–12	0.34±0.05	0,92±0.17	2.72 times
12–24	0.40±0.06	0.66±0.14	1.66 times
10–24	0.41±0.05	1.01±0.17	2.4 times

DISCUSSION

Patients in this study had the same types of operation and anaesthetic technique as those studied by Chakravarty and others (1979). Both groups used the Cardiff Palliator to provide pain relief after operation, and mean pethidine consumption was similar—9.05 $mg\,kg^{-1}$ per 24 h in the earlier study and 9.94 $mg\,kg^{-1}$ per 24 h in the group reported here. Patients using these infusion systems do not consume excessive amounts of drug—a mean pethidine consumption of 9.94 $mg\,kg^{-1}$ per 24 h is equivalent to 116 mg every 4 h in a 70-kg patient.

Mean analogue pain scores after meptazinol and pethidine were almost identical at 43.1 and 42.7 respectively. Given that the overall degree of pain relief was the same, we propose that an indication of relative potency of the drugs can be derived from the amounts of analgesic consumed. The meptazinol : pethidine consumption ratios ranged from 4.5 : 1 to 1.6 : 1 at varying times after surgery, with a mean over 24 h of 2.4 : 1. This result seems to be at variance with the conclusion of Paymaster (1977), who suggested that the drugs were equipotent; however our study and his are not strictly comparable as two different techniques of drug administration were used, and the patients were dissimilar. Paymaster administered meptazinol i.m. and investigated a group of patients who had undergone lower abdominal and orthopaedic surgery. Upper abdominal wounds cause severe pain and high analgesic requirement (Parkhouse, Lambuchts and Simpson, 1961; Swerdlow, Starmer and Daw, 1964).

One patient using meptazinol was removed from the trial because of inadequate analgesia; before this he recorded the highest drug consumption rate in the group, but still gave high pain, nausea and dizziness scores, despite the administration of an anti-emetic. Examination of this patient's demand record showed that the rate of analgesic consumption had been limited by the pre-set minimum interval between doses. It is probable that if he had been permitted to consume more drug, the degree of pain relief would have been greater.

Patients receiving meptazinol had significantly higher scores for nausea than those receiving pethidine. This is consistent with previously published observations (Oosterlinck and deSy, 1975; Gibbs and Johnson, 1980). No evidence of dysphoria was seen with either drug, and no patient reported unpleasant dreams.

Meptazinol behaves as a potent analgesic, but larger amounts were consumed than would be expected from previously suggested potency ratios, the most likely explanation being that meptazinol is less potent than pethidine. As meptazinol produced more nausea and, perhaps, also more dizziness than pethidine, it does not seem an improvement on pethidine when administered by intermittent i.v. injection. Meptazinol however, was shown by Jordan and others (1979) to produce less respiratory depression than morphine when given to conscious volunteers by i.m. injection in doses considered to be equianalgesic: meptazinol 100 mg, and morphine 10 mg (which is roughly comparable to pethidine 100 mg). If this advantageous comparison with traditional analgesics on i.m. injection holds true when meptazinol is given i.v. in the higher doses (2.4 ×) found to be equianalgesic with pethidine in this study, meptazinol may still prove a safe and useful drug in the control of severe pain after surgery.

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COMPARAISON DU MEPTAZINOL ET DE LA PETHIDINE ADMINISTRES PAR VOIE INTRAVEINEUSE SUR DEMANDE POUR LE SOULAGEMENT DES DOULEURS POSTOPERATOIRES

RESUME

On a comparé le meptazinol et la péthidine, au cours d'une étude à double inconnue effectuée sur 20 patients, en utilisant un système analgésique sur demande permettant de soulager la douleur après toute intervention chirurgicale à la partie supérieure de l'abdomen. Le degré d'analgésie, estimé d'une manière subjective, a été satisfaisant aussi bien avec le meptazinol qu'avec la péthidine; bien que le meptazinol ait produit davantage de nausées que la péthidine ($P < 0,01$), il n'y a eu aucune différence significative du point de vue statistique dans la fréquence des autres effets secondaires. Sur une période de 24 h la consommation moyenne de meptazinol a été de 2,4 fois plus élevée que celle de péthidine, ce qui laisse penser que lorsqu'il est administré en injection, le meptazinol est moins puissant que la péthidine.

VERGLEICH ZWISCHEN WUNSCHGEMÄSS ZUR POSTOPERATIVEN SCHMERZLINDERUNG INTRAVENÖS GEGEBENEN DOSEN VON MEPTAZINOL UND PETHIDIN

ZUSAMMENFASSUNG

Metazinol und Pethidin wurden unter Doppelblind-Bedingungen bei 20 Patienten verglichen, bei Verwendung eines Schmerzlinderungssystems auf Wunsch nach Operationen im oberen Unterleib. Das subjektiv bewertete Ausmass der Schmerzlinderung war bei beiden Drogen zufriedenstellend: obwohl Meptazinol wesentlich mehr Übelkeit bewirkte als Pethidin ($P<0,01$), gab es keine statistisch wesentlichen Unterschiede in der Häufigkeit anderer Nebenerscheinungen. Über 24 Stunden betrug de Durchschnittsverbrauch von Meptazinol um 2,4-mal mehr als von Pethidin, was zeigt, das intravenös gegebenes Meptazinol weniger stark wirkt als Pethidin.

COMPARACION DEL MEPTAZINOL Y DE LA PETIDINA ADMINISTRADAS INTRAVENOSAMENTE SEGUN LA DEMANDA PARA LA GERENCIA DEL DOLOR POSOPERATIVO

SUMARIO

Se compararon el meptazinol y la petidina en 20 pacientes y bajo condiciones de doble anonimato mediante un sistema analgésico de administración según la demanda, para aliviar el dolor después de operación quirúrjica del abdomen superior. El grado de anestesia, evaluado subjetivamente, fue el adecuado tanto para el meptazinol como para la petidina; aunque aquel produjo nauseas de una forma más significativa que lo hizo la petidina ($P<0,01$) no hubo una diferencia estadistica significativa en la frecuencia de otros efectos secundarios durante 24 horas. El consumo medio de meptazinol fue 2,4 veces mayor que el de petidina, lo que sugiere cuando la administración es intravenosa aquel es menos potente que ésta.

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EXTRADURAL ANALGESIA: THE INFLUENCE OF VOLUME AND CONCENTRATION OF BUPIVACAINE ON THE MODE OF DELIVERY, ANALGESIC EFFICACY AND MOTOR BLOCK

J. THORBURN AND D. D. MOIR

SUMMARY

Five hundred and seventeen women in labour receiving extradural analgesia, using bupivacaine plain solution, were randomly allocated to one of three groups. Group A received 6–8 ml of 0.5% solution, group B 10–14 ml of 0.25% solution, and group C 6–8 ml of 0.25% solution. Spontaneous delivery occurred in 31.7% of patients in group A, 38.7% in group B and 53% in group C ($P<0.001$). The percentage of rotational forceps, ventouse and Caesarean section deliveries was similar in the three groups. Analgesia was most effective in group A, and least in group C, both during labour and at delivery, although assessment by linear analogue score suggested that the differences between the three groups were slight. Motor block was most frequent and rapidly progressive in groups A, but was progressive in all groups, and after five or more top-up injections, was similar in the three groups. Difficulties with micturition following delivery were significantly more common in group A.

Extradural analgesia is the most effective method of pain control in labour, but its influence on the mode of delivery is controversial. It is argued that patients who require extradural analgesia for the relief of pain in labour are those who would, in any case, have longer and more difficult labours and are more likely to require instrumental delivery. Hoult, MacLennan and Carrie (1977) observed a significant increase in the frequency of instrumental delivery and fetal malposition in patients receiving extradural analgesia. However, Jouppila and colleagues (1979), using low-dose continuous segmental extradural analgesia, were unable to find any increase in the frequency of fetal malposition and suggested that the low-dose technique retained the tone of the pelvic floor muscles thus encouraging rotation of the presenting fetal part. This evidence would suggest that the mode of delivery could be influenced by the choice of agent such that the use of larger volumes or more concentrated solutions might affect adversely the frequency of spontaneous delivery and fetal malposition.

The effect of lumbar extradural analgesia, using 0.25% and 0.5% bupivacaine without adrenaline, on the mode of delivery, the analgesic efficacy, the frequency and the severity of the associated motor block and the frequency of difficulties of micturition has been assessed in the present study.

PATIENTS AND METHODS

Five hundred and seventeen patients who received continuous lumbar extradural analgesia were randomly allocated to one of three groups. Patients in group A received 0.5% bupivacaine 6–8 ml as analgesic agent, for the initial dose and subsequent top-up injections; patients in group B received 0.25% bupivacaine 10–14 ml and patients in group C 0.25% bupivacaine 6–8 ml. Thus, patients in group A and C received similar volumes but differing doses of the drug, and those in groups A and B differing volumes but similar doses of the drug. Extradural analgesia was produced in the same way in all three groups and was instituted when labour became painful. Top-up injections were given when pain recurred.

The extradural puncture was performed in the sitting position, the first injection being given partly through the Tuohy needle and the remainder through the catheter. The patient was then positioned on her side. The use of the unmodified supine position was proscribed at all times, and top-up injections were given with the patient in the lateral position. Patients were encouraged to lie on alternate sides at intervals.

An unblocked segment was recorded when pain was experienced in a localized site, such as the groin, during an otherwise successful block. The occurrence of persistent rectal or perineal pain was noted as an unblocked segment. A unilateral block was recorded when analgesia was present on one side only, and hypotension was recorded if the

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systolic arterial pressure was reported as 90 mm Hg or less following institution of the block.

A standard questionnaire was completed and the patient interviewed 24–48 h after delivery by the author who had not performed the block. The age, parity, induction and duration of labour and the mode of delivery were recorded. At interview, enquiry was directed to the patient's assessment of the pain experienced following initiation of the block, during labour and at delivery. Assessment of the pain was performed in two ways. First, the patient was asked to describe the relief of pain experienced as "complete", "helpful" or "no help" and second, she was requested to complete a 10-cm linear analogue pain score.

Assessment of the motor block was made subjectively by the patient and four grades were recorded. Grade 1 = the patient complained spontaneously of leg weakness; grade 2 = on questioning the patient admitted to finding the leg weakness experienced distressing; grade 3 = leg weakness admitted on enquiry; grade 4 = no weakness noted by the patient.

The frequency of postpartum bladder catheterization was also recorded.

Statistical analysis was performed using Student's *t* test and χ^2 test where appropriate.

RESULTS

The number of patients in the three groups, the mean ages, the proportion of primigravid patients and the frequency of induction of labour are presented in table I. The duration of labour was the same in all three groups, and the patients in groups A and C received similar mean volumes of analgesic solution at each injection. The mean volume of analgesic solution given to patients in group B was 10.66 ml.

Method of delivery

A striking and significant increase in the spontaneous delivery rate was observed in the patients in the low-dose 0.25% bupivacaine group, 53% of whom delivered spontaneously (table II). In groups A and B the spontaneous delivery rate was 32% and 38% respectively; this difference was not significant. Forceps delivery from the occipito–posterior and the occipito–transverse positions occurred in 8%, 9.2% and 7.6% of deliveries in groups A, B and C respectively, and there were no significant differences between the groups. The frequency of low-cavity and mid-cavity forceps delivery was not significantly different in groups A and B, but was significantly less in group C.

TABLE I. *Number of patients in each group, mean age, duration of labour, volume injected, number of injections of bupivacaine, percentage of induced labours and primigravidae (Mean ± 1 SD). Group A = 0.5% bupivacaine 6–8 ml; B = 0.25% bupivacaine 10–14 ml; group C = 0.25% bupivacaine 6–8 ml*

	Group A	Group B	Group C
Number	161	173	183
Mean age (yr)	25.6 ± 5.2	25.7 ± 5.4	25.3 ± 4.98
Duration of labour (h)	11.27 ± 4.57	10.9 ±5.86	10.8 ±4.85
No. doses per patient	3.1 ± 1.6	2.87 ± 1.62	3.77 ± 4.85
Mean dose (ml)	7.46	10.66	7.61
Induced (%)	58	50	62
Primigravida (%)	63	66	69
Apgar scores (%)			
1–4	5.7	4.1	2.1
5–6	7.0	5.3	8.5
7–10	87.4	90.4	89.0

Pain relief

The proportion of patients receiving "no help" from the extradural block during the first stage of labour was 8.8% in group C, and this was significantly greater than in the other two groups, between which there was no difference (table III). Complete pain relief was experienced by 74% and 72.9% of patients in groups A and B, but by only 59.4% of patients in group C. When pain was evaluated by the linear analogue, the patients in group C were seen to have received less effective analgesia (fig. 1, table IV).

The pain experienced at delivery was greatest in the low-dose 0.25% bupivacaine group, but the number of patients receiving "no help" from their block at delivery was not significantly different in the three groups. Relief of pain was clearly greater in the 0.5% bupivacaine group, 64% of patients experiencing complete relief of pain compared with only 46% and 38.1% of patients in groups B and C respectively, these differences being significant (table V). Using the linear analogue score, 0.5% bupivacaine was noted to be significantly more effective in decreasing the pain experienced at delivery than the 0.25% solution, but the difference between groups B and C was not significant (fig. 1, table IV), and the pain

TABLE II. *Mode of delivery*

Mode of delivery	Group A	Group B	Group C	*P* value, χ^2 test A *v*. *B*	*B v*. C	A *v*. C
Number	161	173	183			
Spontaneous vertex delivery (%)	31.7	38.7	53	n.s.	<0.001	<0.001
Low-cavity forceps delivery (%)	14	12.7	7.6	n.s.	<0.001	<0.02
Mid-cavity forceps delivery (%)	27	22.5	15.8	n.s.	<0.05	<0.001
Rotation (%)	8	9.2	7.6	n.s.	n.s.	n.s.
Ventouse (%)	2	2.8	2.7	n.s.	n.s.	n.s.
Caesarean section (%)	17	13.8	13.1	n.s.	n.s.	n.s.

TABLE III. *Patient's assessment of pain relief in labour*

Relief	Group A	Group B	Group C	*P* value, χ^2 test A *v*. B	B *v*. C	A *v*. C
Complete (%)	74	72.9	59.4	n.s.	<0.01	<0.01
Helpful (%)	23	23.5	31.6	n.s.	<0.01	<0.01
No help (%)	3	3.5	8.8	n.s.	<0.01	<0.01 (Yates)

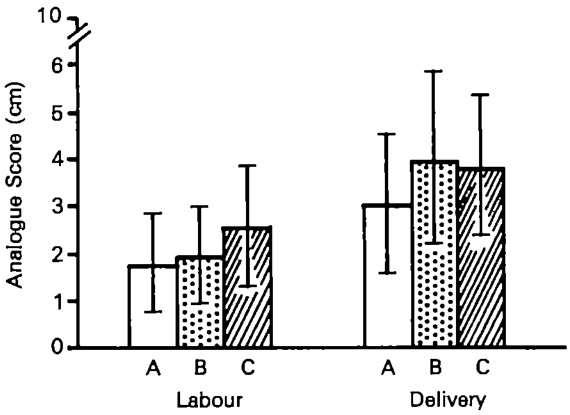

FIG. 1. Linear analogue score from the three groups, during labour and at delivery (mean ± 1SD).

TABLE IV. *Statistical evaluation of the three groups during labour and at delivery, and between labour and delivery* (*Student's* t *test,* P *values*)

Group	A *v*. B	B *v*. C	A *v*. C
Labour	n.s.	<0.005	<0.005
Delivery	<0.02	n.s.	<0.02
Group	A	B	C
Labour *v*. delivery	<0.001	<0.001	<0.001

experienced at delivery was significantly greater in all three groups than that experienced in the first stage of labour.

Motor block

Significantly fewer patients (42.6%) in group C, experienced motor weakness than in the other two

TABLE V. *Patient's assessment of pain relief at delivery*

				P value, χ^2 test		
Relief	Group A	Group B	Group C	A *v.* B	B *v.* C	A *v.* C
Complete (%)	64	46	38.1	<0.01	<0.01	<0.001
Helpful (%)	21	33.7	41.3	<0.01	n.s.	<0.001
No help (%)	15	19.5	20.6	n.s.	n.s.	n.s.

TABLE VI. *Patient's assessment of motor weakness*

				P value, χ^2 test		
Motor weakness	Group A	Group B	Group C	A *v.* B	B *v.* C	A *v.* C
Grade I (%)	2	1.2	1	n.s.	n.s.	n.s.
Grade II (%)	11	3.6	2.1	<0.001	n.s.	<0.001 (Yates)
Grade III (%)	53	51.8	39.5	n.s.	<0.01	<0.001
Grade IV (%)	34	43.2	57.1	<0.02	<0.001	<0.001

TABLE VII. *Number of patients delivered in each groups, related to the number of injections of bupivacaine before delivery*

	No. patients in each group			P value, χ^2 test		
No. injections of bupivacaine	Group A	Group B	Group C	A *v.* B	B *v.* C	A *v.* C
1–2	53	84	57	<0.001	<0.001	n.s.
3–4	74	60	73	<0.001	n.s.	<0.02
≥5	21	26	52	n.s.	0.001	0.001

TABLE VIII. *Number and percentage of patients experiencing leg weakness, related to the number of injections of bupivacaine before delivery*

	No. patients in each group			P value, χ^2 test		
No. injections of bupivacaine	Group A	Group B	Group C	A *v.* B	B *v.* C	A *v.* C
1–2	25 (47.2%)	39 (46%)	13 (22%)	n.s.	<0.001	<0.001
3–4	54 (73%)	35 (58%)	27 (36%)	<0.05	<0.01	<0.001
≥5	18 (85%)	23 (88.4%)	37 (71%)	n.s.	n.s.	n.s.

TABLE IX. *Frequency of complications occurring during labour in each group, and the frequency of postpartum catheterization*

				P value, χ^2 test		
	Group A	Group B	Group C	A *v.* B	B *v.* C	A *v.* C
Hypotension (%)	3.8	6.9	4.9	n.s.	n.s.	n.s.
Unblocked segments (%)	6.2	6.3	9.2	n.s.	n.s.	n.s.
Unilateral block (%)	16.1	5.2	13.6	<0.01	<0.02	n.s.
Catheterized (%)	24	13	15	<0.01	n.s.	<0.02

groups, and a significantly greater number of patients in group A noted leg weakness than in the other two groups (table VI). The number of patients experiencing leg weakness of grades 2 and 3 was greater in group A than in group C, but the number of patients complaining spontaneously of motor weakness was the same in all three groups. A significantly greater number of patients in the low-dose group received more than five injections of local anaesthetic when compared with patients in the other two groups (table VII). When the number of patients experiencing motor weakness was related to the number of injections given (table VIII), the onset was earlier and progressed more rapidly in the patients receiving 0.5% bupivacaine than in the other two groups, but after five top-up injections no significant differences were observed between the three groups.

The frequency of catheterization of the bladder after delivery was greater in the patients receiving 0.5% bupivacaine. A greater number of patients in the large volume group developed systemic hypotension, but the difference was not significant. The frequency of unilateral block was significantly less in this group (group B). Complications in each group are summarized in table IX.

DISCUSSION

The use of small volumes of 0.25% bupivacaine without adrenaline for lumbar extradural analgesia was associated with a significant increase in the number of spontaneous deliveries, but the analgesia provided was less effective than that produced by larger volumes or a greater concentration of the same drug. The use of 0.5% bupivacaine resulted in the most effective analgesia, but was associated with the greatest frequency of instrumental deliveries. The frequency of rotational forceps delivery was not influenced by either the volume or the concentration of the solution in use, but the onset and severity of motor block were related to the volume and the concentration in use, and to the number of top-up injections.

It is appropriate to consider briefly the mode of delivery in patients who did not receive extradural analgesia. In the first 3 months of the trial, 507 (61%) labours were managed without extradural analgesia. The population and method of delivery are shown in table X.

TABLE X. *Population and method of delivery during the trial*

	Non-extradural group	Extradural group
Primigravidae (%)	28.6	63–69
Duration of labour (h)	4.8	10.8–11.27
Induced (%)	59	50–62
Spontaneous delivery (%)	86	31.7–53
Low-cavity forceps (%)	4.1	7.6–14
Mid-cavity forceps (%)	3.6	15.8–27.0
Ventouse (%)	0.6	2.0–2.8
Caesarean section (%)	1.9	13.1–17.0
Average duration of labour before block (h)		5.3

Clearly the population and the mode of delivery were different in the non-extradural group. The labours were shorter, operative delivery much less common and a greater proportion of patients were parous. Patients selected to receive extradural analgesia were experiencing unusually severe pain associated with a long labour, perhaps as a result of an abnormality of labour such as fetal malposition or a minor degree of cephalo–pelvic disproportion. The high percentage of primigravidae in the extradural groups would predispose to longer labours and a greater frequency of forceps delivery.

Extradural analgesia has been associated by Raabe and Belfrage (1976) and Hoult, MacLennan and Carrie (1977), with an increase in the rate of instrumental delivery and an increase in the frequency of fetal malposition and rotational forceps delivery. In Hoult's series 19.4% were delivered from the occipito–transverse or occipito–posterior positions, and this was ascribed to the motor block accompanying effective extradural analgesia causing relaxation of the pelvic floor muscles, with failure of the presenting fetal part to rotate. Doughty (1969) suggested that if extradural analgesia was used for pain relief in normal labour, and the block confined to the 11th and 12th thoracic segments, 80% of patients could achieve a spontaneous delivery. Maltau and Anderson (1975) using low-dose continuous extradural analgesia, and Jouppila and colleagues (1979), did not observe an increase in the fetal malposition or instrumental delivery rate, and related this to the segmental nature of the block which retained the tone of the pelvic floor muscles. None of these investigators assessed the frequency or the severity of the motor block. However, both Challen and colleagues (1977) and Littlewood and co-workers (1977) observed that motor weakness became more common and intense as the concentration of the local anaesthetic agent increased.

The frequency of instrumental delivery varied in Challen's series, but the variation was not statistically significant.

If rotation occurred solely as a result of the tone of the pelvic floor muscles, then fetal malposition would occur in all patients with severe motor weakness, but this was not observed. The mechanisms of the second stage of labour are understood, but the precise relationships of the factors involved are not. The shape of the fetal head and the changing planes of the widest diameter of the maternal pelvis as the fetal head descends are other factors. The fetal head takes the path of least resistance and rotates. Both instrumental delivery and severe motor block were more common in patients who experienced the most effective analgesia. The result of this more profound block may be to obtund the reflex urge to push and the patient's ability to push, and these may result in an increase in the frequency of forceps delivery.

Arbitrary limitation of the duration of the second stage of labour is probably no longer appropriate when continuous monitoring of the fetal heart rate confirms that the fetus is in good condition. Safe prolongation of the second stage may allow further descent and perhaps rotation of the fetal head, thereby converting a difficult forceps delivery into an outlet forceps delivery or even a spontaneous vertex delivery. Although Livnat and colleagues (1978) have shown that fetal acidosis is no greater after a low-cavity forceps delivery than after spontaneous vertex delivery, the wish of the mother to deliver her baby by her own efforts should be respected when this can be done with safety.

The use of a larger volume of 0.25% bupivacaine resulted in slightly improved analgesia in the first stage of labour and a more rapid onset of motor block than that observed in the small volume group, but with a significant increase in the frequency of instrumental delivery. In addition, its use resulted in a decrease in the number of patients experiencing a unilateral block and an increase (not significant) in the number exhibiting hypotension.

The number of patients catheterized for painless retention of urine in the period after delivery was significantly increased in group A, but not in groups B and C. The percentage of instrumental deliveries was significantly increased in patients in group B, and if micturition difficulties were related to trauma to the bladder trigone occurring during forceps delivery, then an increase would have occurred in this group. This observation suggests that the concentration of the drug used may be a factor influencing the frequency of difficulties of micturition after delivery.

It has been shown that the use of 0.25% bupivacaine 6–8 ml provided "complete relief" of pain for 59.4% of patients in the first stage of labour and for 38.1% at delivery. Similar results were observed using a linear analogue pain score. It is our belief that the use of small volumes of 0.25% bupivacaine offer considerable advantages in terms of the high spontaneous delivery rate and unwanted side-effects, although the frequency of effective analgesia is decreased. If the analgesia is inadequate, the volume of top-up injections can be increased readily, and failing that the concentration of the solution can be increased.

For the woman who wishes, if possible, to deliver her child by her own efforts and yet to receive a useful, if not complete, measure of pain relief then 0.25% bupivacaine should be used in volumes of 6–8 ml. This would also minimize the likelihood of distressing motor blockade and postpartum difficulties of micturition. The woman who wishes the best possible analgesia and is willing to accept the increased probability of a forceps delivery, motor blockade and difficulties with micturition should be offered extradural analgesia with 0.5% bupivacaine.

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ANALGESIE EXTRADURALE: L'INFLUENCE DU VOLUME ET DE LA CONCENTRATION DE BUPIVACAINE SUR LE MODE D'ACCOUCHEMENT, L'EFFICACITE ANALGESIQUE ET LE BLOCAGE MOTEUR

RESUME

On a réparti au hasard en trois groupes cinq cent dix-sept femmes parturientes auxquelles on avait administré une solution simple de bupivacaine pour provoquer l'analgésie extradurale. On administra au Groupe A 6–8 ml de solution à 0,5%, au groupe B 10–14 ml de solution à 0,25% et au groupe C 6–8 ml de solution à 0,25%. L'accouchement spontané s'est produit chez 31,7% des patientes du groupe A, chez 38,7% dans le groupe B et chez 53% dans le groupe C ($P < 0{,}001$). Le pourcentage d'accouchements au forceps, à la ventouse et par césarienne était analogue dans les trois groupes. L'analgésie fut la plus efficace chez le groupe A et le moins dans le groupe C, soit au cours des douleurs soit au cours de l'accouchement, bien que l'évaluation par marques analogues linéaires puisse impliquer que les différences entre les trois groupes furent légères. Le blocage moteur a été le plus fréquent et rapidement progressif chez le groupe A, mais il fut progressif chez tous les groupes, et à la suite de cinq ou plus encore d'injections complémentaires, il était semblable dans les trois groupes. Des difficultés de micturition après l'accouchement furent beaucoup plus fréquentes chez le groupe A.

EXTRADURALE ANALGESIE: DER EINFLUSS VON VOLUMEN UND KONZENTRATION VON BUPIVACAIN AUF DIE GEBURTSWEISE, SCHMERZLINDERNDE WIRKUNG UND MOTORISCHE BLOCKIERUNG

ZUSAMMENFASSUNG

Fünf hundert und siebzehn Frauen in Geburtswehen, die einfache Bupivacain-Lösungen für extradurale Analgesie erhielten, wurden willkürlich in eine von drei Gruppen zugeteilt. Gruppe A erhielt 6–8 ml einer 0,5%igen Lösung, Gruppe B 10–14 ml einer 0,25%igen Lösung und Gruppe C 6–8 ml einer 0,25%igen Lösung. Spontane Geburt erfolgte bei 31,7% der Frauen in Gruppe A, bei 38,7% in Gruppe B und bei 53% in Gruppe C ($P < 0{,}001$). Der Prozentsatz von Zangen-, Schröpfkopf- und Käiserschnittgeburten war in den 3 Gruppen ähnlich. Analgesie war am wirksamsten in Gruppe A, am geringsten in Gruppe C, sowohl während der Wehen als such bei der Geburt, wenn auch lineare Analogbewertung nur geringfügige Unterschiede zwischen den drei Gruppen zeigte. Die Motorblockierung war am häufigsten und schnellsten progressiv in Gruppe A, war aber progressiv in allen Gruppen, und nach fünf oder mehr weiteren Injektionen auch ähnlich in allen Gruppen. Schwierigkeiten beim Harnlassen nach der Geburt waren häufiger in Gruppe A.

ANALGESIA EXTRADURAL: INFLUENCIA DEL VOLUMEN Y CONCENTRACIÓN DE BUPIVACAINA SOBRE EL MODO DE PARTO, LA EFICACIA DE LA ANALGESIA Y EL BLOQUEO MOTOR

SUMARIO

Se distribuyeron al azar entre tres grupos a quinientos diez y siete mujeres parturientes a las cuales fue administrada una solución simple de bupivacaina para inducir una analgesia extradural. Se administró 6–8 ml de solución al 0,5% al grupo A, 10–14 ml de solución al 0, 25% al grupo B y 6–8 ml de solución al 0,25% al grupo C. Se produjo el parto espontáneo en un 31,7% de las pacientes del grupo A, en un 38,7% de las del grupo B y en un 53% de las del grupo C ($P < 0{,}001$). El porcentaje de partos mediante fórceps rotatorio, ventosa y cesárea fue similar en los tres grupos. La analgesia fue más eficaz en el grupo A, y menos efectiva en el grup C, tanto durante los dolores anteriores al parto como en el curso del mismo, aunque la evaluación por marcas análogas lineares hiciera pensar que las diferencias entre los tres grupos fueren menores. El bloqueo motor fue más frecuente y rápido y progresivo en el grupo A, pero fue progresivo en todos los grupos y luego de cinco o más inyecciones complementarias, fue similar en los tres grupos. Las pacientes del grupo A experimentaron dificultades de micturición después del parto mucho más frecuentes.

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HORMONAL RESPONSES TO HIGH-DOSE FENTANYL ANAESTHESIA

A study in patients undergoing cardiac surgery

P. S. SEBEL, J. G. BOVILL, A. P. M. SCHELLEKENS AND C. D. HAWKER

SUMMARY

The hormonal responses to anaesthesia and cardiac surgery were studied in 20 patients. Ten patients were anaesthetized with fentanyl 60 µg kg^{-1} and nitrous oxide in oxygen and 10 with etomidate 0.3 mg kg^{-1} and nitrous oxide in oxygen plus halothane. There were no significant changes in cortisol, growth hormone or insulin concentrations in response to surgery in either group, although cortisol concentrations decreased during cardiopulmonary bypass. Both groups showed increases in prolactin concentrations. Patients anaesthetized with etomidate and halothane showed a significant increase in adrenaline and glucose concentrations not seen in the fentanyl group. Cardiopulmonary bypass was associated with marked increases in catecholamines in both groups.

Fentanyl 50–100 µg kg^{-1} has been shown to produce adequate anaesthesia with minimal changes in cardiovascular dynamics in patients undergoing cardiac surgery (Stanley and Webster, 1978) and, when used as a supplement (50 µg kg^{-1}) to thiopentone, nitrous oxide and oxygen, will decrease the metabolic and hormonal responses to gynaecological surgery (Hall et al., 1978). Although the effects of surgery on the antidiuretic hormone are suppressed by fentanyl, those of cardiopulmonary bypass are not (Stanley, Philbin and Coggins, 1979). Likewise, although the catecholamine response to surgery is suppressed by fentanyl 75 µg kg^{-1}, marked increases occur during cardiopulmonary bypass (Stanley et al., 1980). Since catecholamines increase myocardial oxygen consumption by their chronotropic and inotropic actions (Graham et al., 1967), the suppression of this response would be beneficial to patients with severe coronary artery disease undergoing surgery. We have studied the hormonal and metabolic responses to fentanyl 60 µg kg^{-1} used as an anaesthetic for cardiac surgery and compared them with an anaesthetic technique not using narcotic analgesics.

TABLE I. *Details of patients*

						Type of operation			
	No.	M	F	Age (yr) (± SEM)	Weight (kg) (± SEM)	Valve	Coronary	Valve + CA	Aneurysm + CA
Fentanyl group	10	9	1	63.5(±2.18)	74.6(±3.53)	1	8	1	—
Etomidate/halothane group	10	8	2	55.6(±3.11)	75.9(±3.4)	1	7	—	2

PATIENTS AND METHODS

Twenty patients undergoing cardiac surgery involving cardiopulmonary bypass were studied. Those patients scheduled for coronary artery grafts were all receiving beta-blocking drugs and nitrates for the control of angina pectoris and those undergoing valve replacements were receiving digoxin and diuretics to control congestive cardiac failure. All medication, except nitrates, was discontinued the evening before surgery. Details of the patients and type of operation are shown in table I.

All patients were premedicated with lorazepam 4 mg orally 1.5 h before the scheduled time of operation. In the operating theatre, two peripheral infusions, a radial artery cannula and a wide-bore central venous catheter (via external jugular vein) were inserted under local anaesthesia. E.c.g. electrodes were applied.

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The patients were randomly divided into two groups of 10 patients each. In the first (fentanyl) group, anaesthesia was induced with fentanyl 60 µg kg^{-1} i.v. over a 2-min period and continued with 50% nitrous oxide in oxygen. In the second (halothane) group, anaesthesia was induced with etomidate 0.3 mg kg^{-1} and continued with 50% nitrous oxide in oxygen and halothane as required. Both groups received pancuronium 8 mg to produce neuromuscular blockade. Respiration was assisted and then controlled manually using a face-mask. Five minutes after induction of anaesthesia, the trachea was intubated and thermocouple probes inserted into the oesophagus, nasopharynx and triceps muscle to monitor body temperature. A nasogastric tube was inserted and the bladder catheterized. During anaesthesia, ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.5–5%. An arterial blood sample was taken within 30 min of induction for blood-gas analysis and served as an assessment of the adequacy of ventilation.

Cardiopulmonary bypass was conducted using a Polystan Rygg–Kyvsgaard 5000 bubble oxygenator with moderate hypothermia (24 °C) and haemodilution to a haematocrit of 20–25%. Pump flow was maintained at 55 ml kg^{-1} min^{-1}. The carbon dioxide concentration in the expiratory vent of the oxygenator was kept at a constant 6%, corresponding to Pa_{CO_2} 6 kPa.

In the fentanyl group, fentanyl 1 mg was added to the pump prime immediately before the start of bypass. In the halothane group, 0.5% halothane was added to the oxygenator throughout the period of bypass. Venous blood samples were withdrawn from the central venous catheter. Sampling times are shown in table II. From each blood sample a 5-ml aliquot of blood (for adrenaline, noradrenaline and dopamine assay) was added to a tube containing glutathione and EGTA (ethylene-glycol-bis (β-aminoethyl)-N,N′ tetraacetic acid) and the tube placed in an ice-water bath. The sample was immediately centrifuged using ice-filled centrifuge cups and the plasma placed in a screw-topped plastic container which was frozen to −26 °C and stored until assayed. Ten millilitre of blood was injected into a lithium–heparin tube (for measurement of the concentrations of insulin, growth hormone cortisol and prolactin), centrifuged and the plasma stored at −26 °C. In the fentanyl group 10 ml of blood was taken into a lithium–heparin tube before bypass and 15 min on bypass for the estimation of plasma fentanyl concentration. Two millilitre of blood was added to a tube containing potassium oxalate and sodium fluoride and immediately analysed for blood glucose concentration.

TABLE II. *Sample times*

Sample 1	Before induction (after cannulation)
Sample 2	5 min after induction
Sample 3	5 min after intubation
Sample 4	2 min after incision
Sample 5	5 min after sternotomy
Sample 6	Before bypass (aortic cannulation)
Sample 7	15 min on bypass
Sample 8	60 min on bypass (or release aortic cross clamp whichever earlier)

All assays were carried out in duplicate. Glucose was measured with an IL 919 blood glucose analyser (Instrumentation Laboratories) using a modification of the glucose oxidase/peroxidase method (Trinder, 1969). Insulin, growth hormone, cortisol and prolactin concentrations were measured by standard radioimmunoassay techniques (Peake, 1974; Starr and Rubenstein, 1974; Assies, Schellekens and Touber, 1978; Thijssen, van den Berg and Adlercreutz, 1980).

The concentrations of the catecholamines were estimated by radio enzyme assay using a modification of the method described by Peuler and Johnson (1977). Plasma fentanyl concentration was measured by radioimmunoassay (Michiels, Hendriks and Heykants, 1977). Data are presented as mean values ± SEM. Statistical analysis was carried out using analysis of variance. A modified *t* test was used to identify significant differences from control values using critical values for *P* calculated according to the method of Bonferroni (Wallenstein, Zucker and Fleiss, 1980). The plasma fentanyl concentrations were compared using a paired *t* test.

RESULTS

Control values

All control values were within the normal laboratory range except for three patients. One patient had an insulin concentration of 30 mu. litre^{-1} (normal range 5–25 mu. litre^{-1}) which decreased to 16 mu. litre^{-1} immediately after induction and did not increase beyond 18 mu. litre^{-1}. Two patients in the fentanyl group had cortisol concentrations of 0.68 and 0.69 µmol litre^{-1} (normal range 0.16–0.65 µmol litre^{-1}), both of which were within the normal range by the time of incision.

Glucose (fig. 1)

In the fentanyl group, there were no significant changes in blood glucose concentration at any time. In the patients anaesthetized with etomidate and halothane, there was a highly significant change in blood glucose concentration ($F = 6.373$; $P < 0.005$). Compared with control values, the differences were highly significant at samples 6, 7 and 8 ($P < 0.005$)

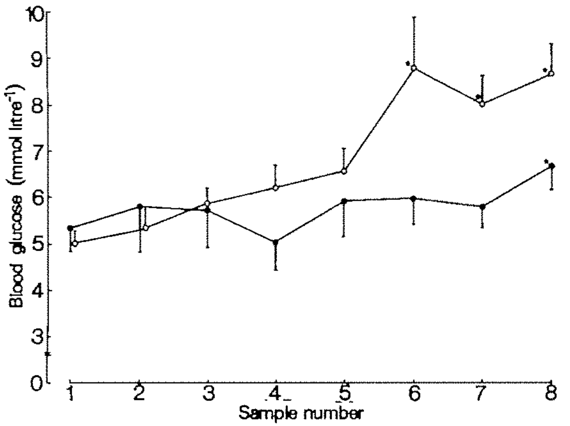

FIG. 1. Change in blood glucose concentration (mmol litre^{-1}) (mean ± SEM). Sample times as in table II. Fentanyl = ●; halothane = ○; $^*P < 0.05$.

Insulin (fig. 2)

The changes in blood glucose concentration were not reflected by insulin suppression. In the period before bypass the insulin concentrations

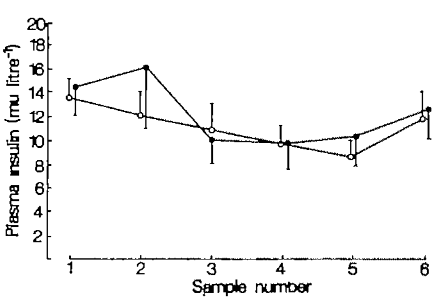

FIG. 2. Change in plasma insulin concentration (mu. litre^{-1}) in the period before cardiopulmonary bypass (mean ± SEM). Sample times as in table II. Fentanyl = ●; halothane = ○.

were not significantly different from control values. No insulin results are available from the period during cardiopulmonary bypass since the assay showed "negative" insulin concentrations. These result from some interference with the assay method, possibly by "Haemaccel", which was used in the prime. This phenomenon is being further investigated.

Cortisol (fig. 3)

Cortisol concentrations decreased after induction in both groups although the difference was only significant ($P < 0.01$) at 15 min on bypass in the fentanyl group and was significant ($P < 0.01$) for both samples on bypass in the halothane group. These significant reductions may have been caused by haemodilution.

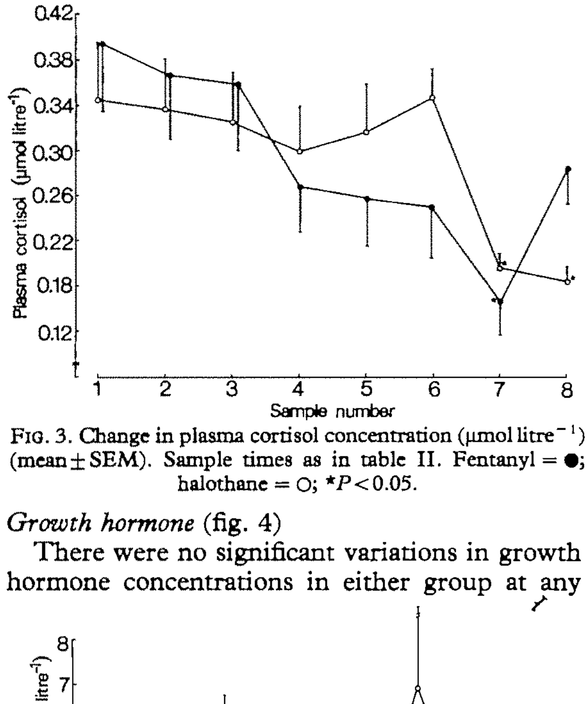

FIG. 3. Change in plasma cortisol concentration (µmol litre^{-1}) (mean ± SEM). Sample times as in table II. Fentanyl = ●; halothane = ○; $^*P < 0.05$.

Growth hormone (fig. 4)

There were no significant variations in growth hormone concentrations in either group at any

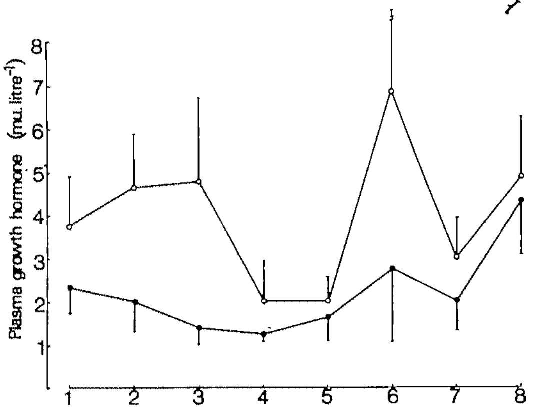

FIG. 4. Change in plasma growth hormone concentration (mu. litre^{-1}) (mean ± SEM). Sample times as in table II. Fentanyl = ●; halothane = ○.

time in the period of the study. The values in the fentanyl group were smaller throughout, but the control value was also lower than in the halothane group.

Prolactin (fig. 5)

Prolactin concentrations increased in both groups, to three times control in the halothane group and five times in the fentanyl group. The concentrations decreased markedly on cardiopulmonary bypass, probably as a result of haemodilution.

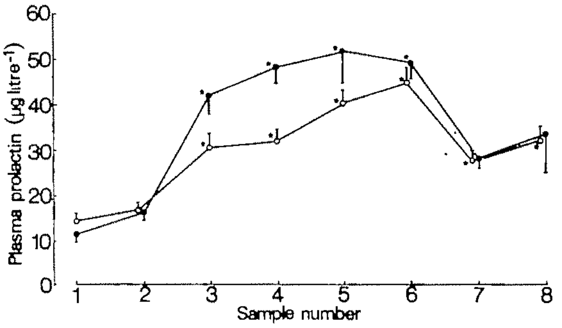

FIG. 5. Change in plasma prolactin concentration (µg litre^{-1}) (mean ± SEM). Sample times as in table II. Fentanyl = ●; halothane = ○; *$P<0.05$.

Catecholmines before bypass (figs 6, 7, 8)

Induction of anaesthesia with fentanyl was associated with a decrease in plasma catecholamine concentrations, although this did not reach significance. In the halothane group, the adrenaline concentrations increased, but became significant only just before bypass in sample 6 ($P<0.005$).

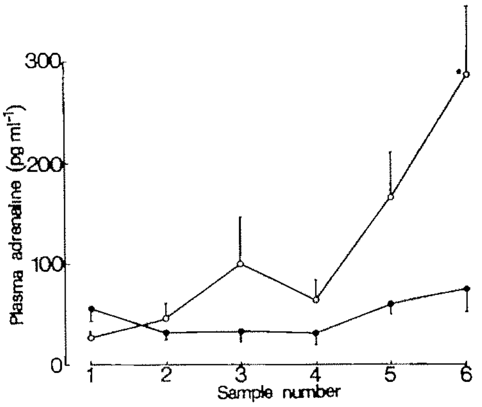

FIG. 6. Change in plasma adrenaline concentration (pg ml^{-1}) in the period before cardiopulmonary bypass (mean ± SEM). Sample times as in table II. Fentanyl = ●; halothane = ○; *$P<0.05$.

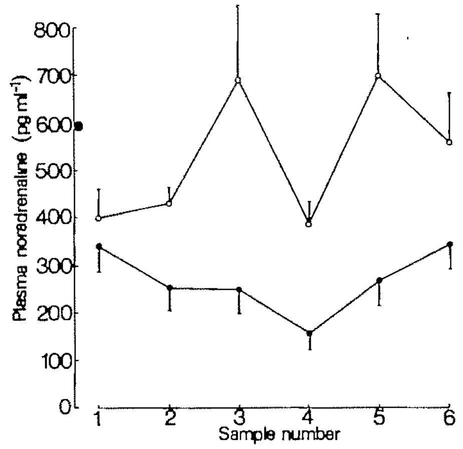

FIG. 7. Change in plasma noradrenaline concentration (pg ml^{-1}) in the period before cardiopulmonary bypass (mean ± SEM). Sample times as in table II. Fentanyl = ●; halothane = ○.

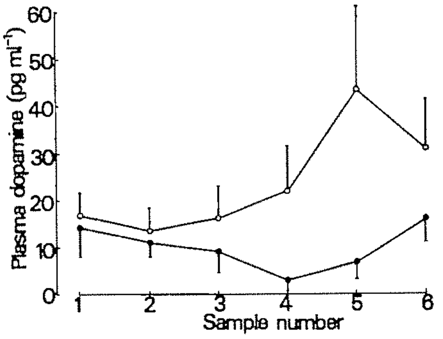

FIG. 8. Change in plasma dopamine concentration (pg ml^{-1}) in the period before cardiopulmonary bypass (mean ± SEM). Sample times as in table II. Fentanyl = ●; halothane = ○.

Noradrenaline concentrations in this group varied widely. In the period before bypass there were no significant changes in dopamine concentrations, although the trend was for the halothane group to be greater.

Catecholamines during cardiopulmonary bypass (fig. 9)

Cardiopulmonary bypass was associated with marked increases in plasma catecholamine concentrations. In the fentanyl group these were highly significant ($P<0.001$) for adrenaline, noradrenaline and dopamine at 1 h on bypass. In the patients anaesthetized with halothane there was a highly significant increase ($P<0.005$) in adrenaline in both samples during bypass.

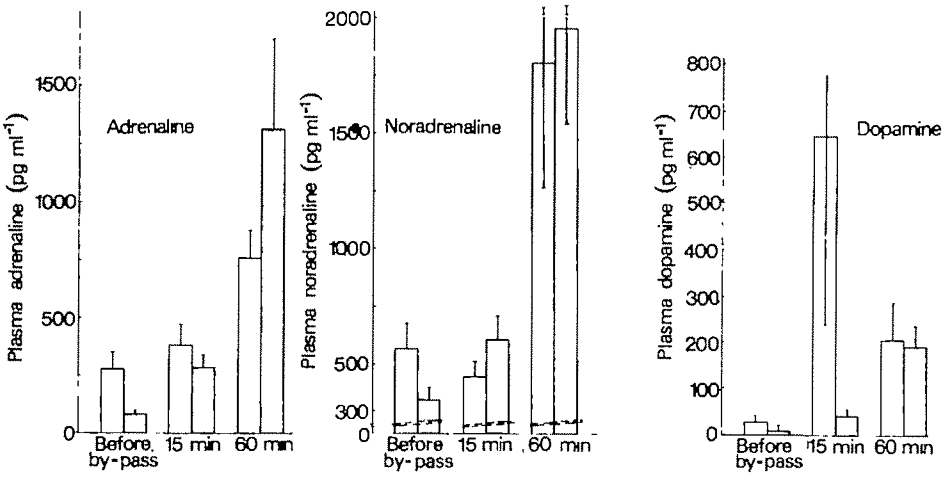

FIG. 9. Change in plasma catecholamine concentration (pg ml^{-1}) during cardiopulmonary bypass (mean ± SEM). Shaded columns = fentanyl; open columns = halothane.

Noradrenaline was significantly increased ($P<0.001$) at 1 h on bypass but not at 15 min. Dopamine was significantly increased ($P<0.05$) at 15 min on bypass but not at 1 h.

Fentanyl

The mean plasma fentanyl concentration before cardiopulmonary bypass was 20.6 (±1.53) ng ml^{-1} and at 15 min on bypass was 16.2 (±0.70) ng ml^{-1}, a significant decrease ($P<0.005$).

DISCUSSION

The neuro-endocrine response is part of the human physiological response to stress (Cannon, 1929). However, this physiological response may have adverse effects on a patient undergoing surgery by increasing the work of the heart and the catabolism of protein (Savege, 1978).

It is possible to modify the neuro-endocrine response to surgical stress by interrupting the afferent pathways by local anaesthetic techniques (Newsome and Rose, 1971). Large doses of morphine have been shown to modify the response to surgery: morphine 1–4 mg kg^{-1} will obtund the increases in plasma cortisol and growth hormone concentrations seen during surgery (George et al., 1974). However, an anti-diuretic hormone response remained during morphine anaesthesia (Philbin et al., 1976). Morphine also produced significant increases in plasma adrenaline and noradrenaline concentrations which correlate with increases in arterial pressure and heart rate (Hasbrouk, 1970). Therefore, morphine anaesthesia modifies, but does not abolish, the endocrine response to surgery.

We have shown that fentanyl 50–70 μg kg^{-1} produces deep surgical anaesthesia (Sebel et al., 1980). Stanley and colleagues have shown in various studies that anaesthesia with fentanyl 50 μg kg^{-1} was an improvement on morphine, producing a high degree of cardiovascular stability (Stanley and Webster, 1978; Lunn et al., 1979; Stanley, Philbin and Coggins, 1979). Hall and coworkers (1978) showed that fentanyl 50 μg kg^{-1}, compared with halothane as a supplement to anaesthesia, significantly decreased the metabolic and endocrine responses to surgery in young healthy women undergoing tubal surgery. They found that fentanyl abolished the hyperglycaemic response to surgery seen during halothane anaesthesia and the findings of our study are in agreement with this observation. However, we were unable to demonstrate the difference between cortisol and growth hormone responses seen in that study. The patients who received halothane in Hall's study showed a marked increase in both plasma growth hormone and cortisol concentrations, whereas the patients who received fentanyl showed no change. We were unable to demonstrate any significant change in growth hormone concentrations in either group. In both our groups, the concentration of cortisol decreased significantly although the decrease was more marked in the fentanyl group. The decrease in cortisol seen in both groups during cardiopulmonary bypass may have been a result of haemodilution. The explanation for the difference in response is probably not related to surgical stress, cardiac surgery being more "stressful" than tubal surgery. It is more likely to be a result of differences in patient groups or premedication. Our patients were older, with pre-existing cardiac disease and were all taking medication including beta-blocking drugs, which may affect endocrine responses.

Although beta-blocking drugs were discontinued on the evening before surgery, in both groups of patients sufficent residual beta blockade may have existed to affect glucose and fat metabolism. No attempt was made during the study to assess the degree of residual blockade that existed on the morning of surgery, although it is likely to have been comparable in the two groups. Because of the problem of residual beta blockade, it is impossible to extrapolate the results of this study to other groups of patients not taking beta blockers. This does not limit the validity of the results with respect to patients undergoing coronary artery surgery, as a very high proportion of these patients will be taking beta blockers. Stanley and others (1980) have reported marked reductions in cortisol concentrations in response to fentanyl anaesthesia. Their patients were not taking beta blockers. In our study two patients had cortisol values just outside the upper limit for normal in our laboratory and one patient had an increased insulin concentration. Since the laboratory normal ranges relate to unstressed patients, it is perhaps to be expected that there would be abnormal control values in some patients on the morning of cardiac surgery, especially following the stress of radial artery, venous and external jugular cannulations.

Prolactin concentration increases fivefold during anaesthesia and surgery, although its significance as part of the stress response is uncertain (Noel et al., 1972). The increase in prolactin concentration may alter the myocardial response to catecholamines and cause tachycardia and arrhythmias (Manku, Nassar and Horrobin, 1973). In our series both groups of patients showed a significant increase in prolactin concentration in the period before bypass period. Prolactin was the only hormone that increased significantly during that period in the fentanyl group. Opiates are known to have a direct stimulating effect on prolactin secretion (Clemens and Shaar, 1980), which may explain the changes seen in this group.

Van der Vusse and others (1979) have shown that fentanyl decreases the energy demand of artificially-induced ischaemic myocardium in dogs and suggested that this is the result of the negative chronotropic effect of fentanyl. We suggest that a decrease in catecholamine secretion may be responsible also. In our study the decrease in catecholamine concentrations did not reach significance, but Stanley and others (1980) found highly significant reductions in both adrenaline and noradrenaline concentrations. Therefore, fentanyl may be beneficial in decreasing myocardial work and thus oxygen requirement. This is important in patients with severe coronary artery disease in whom coronary blood flow is limited. Stanley and co-workers (1980) showed that cardiopulmonary bypass was associated with marked increases in catecholamine concentrations. Following a bolus injection of fentanyl 60 $\mu g\,kg^{-1}$ the plasma fentanyl concentration decreases by about 50% at the start of cardiopulmonary bypass (Bovill and Sebel, 1980). Despite maintaining plasma fentanyl concentrations close to prebypass values (20.6 ($\pm$1.53) $ng\,ml^{-1}$ compared with 16.2 ($\pm$0.70) $ng\,ml^{-1}$), we were unable to eliminate the changes in the concentrations of the catecholamines during cardiopulmonary bypass.

Cardiopulmonary bypass, with non-pulsatile flow, haemodilution and hypothermia is an extremely non-physiological state. Whilst we suspect that it may be possible to modify the endocrine responses to this situation by achieving sufficiently high plasma concentrations of fentanyl, it is likely that this would result in unacceptable respiratory depression following operation.

No attempt has been made to continue the study after cardiopulmonary bypass since there are many uncontrollable factors during this period. Such a study, of the longer term effects of "high-dose" fentanyl anaesthesia, would be more appropriate in non-cardiac major surgery. Therefore, we conclude that anaesthesia with fentanyl 60 $\mu g\,kg^{-1}$ causes a significant decrease in the concentrations of the circulating catecholamines and abolition of hyperglycaemic response to surgery in the period before bypass. This is not maintained during cardiopulmonary bypass.

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RESPONSES HORMONALES A L'ANESTHESIE AU MOYEN DE HAUTES DOSES DE FENTANYL

Une étude chez des patients soumis à des opérations chirurgicales cardiaques

RESUME

On a étudié les réponses hormonales à l'anesthésie et à la chirurgie cardiaque de 20 patients. Dix d'entre eux furent anesthésiés avec 60 µg kg^{-1} de fentanyl et du protoxyde d'azote dans de l'oxygene et les 10 autres avec de l'étomidate en dose de 0,3 mg kg^{-1} et du protoxyde d'azote dans de l'oxygène plus de l'halothane. Il n'y a eu dans aucun des deux groupes de changements significatifs dans le cortisol, le principe de croissance ou les concentrations d'insuline du fait de la réaction à l'intervention chirurgicale, bien que les concentrations de cortisol aient diminué pendant la dérivation cardiopulmonaire. Les deux groupes ont accusé des augmentations de concentrations de prolactine. Les patients anesthésiés à l'aide d'étomidate et d'halothane ont eu une augmentation significative des concentrations d'adrénaline et de glucose que l'on n'a pas constatée dans le Groupe traité au fentanyl. La dérivation cardiopulmonaire a été associée à des augmentations marquées de catécholamines dans les deux groupes.

HORMONALE REAKTIONEN AUF NARKOSE MIT HOHEN DOSEN VON FENTANYL

Eine Studie an Patienten, die sich Herzoperationen unterziehen

ZUSAMMENFASSUNG

Hormonale Reaktionen auf Narkose und auf Herzchirurgie wurden bei 20 Patienten studiert. Zehn Patienten wurden mit Fentanyl 60 µg kg^{-1} und Stickoxyd in Sauerstoff narkotisiert, 10 andere mit Etomidat 0,3 mg kg^{-1} und Stickoxyd in Sauerstoff plus Halothan. Es gab keine signifikanten Veränderungen der Konzentrationen von Hydrocortison, Wachstumshomonen oder Insulin bei beiden Gruppen als Reaktion auf die Operation, obwohl die Hydrocortisonkonzentration während des Herzlungen-Bypass absank. Beide Gruppen zeigten erhöhte Prolaktinkonzentrationen. Mit Etomidat und Halothan narkotisierte Patienten zeigten deutliche Anstiege der Adrenalin- und Glukosekonzentrationen, die es in der Fentanyl-Gruppe nicht gab. Der Herzlungen-Bypass stand mit deutlichen Katecholaminerhöhungen bei beiden Gruppen in Verbindung.

RESPUESTAS HORMONALES A LA ANALGESIA POR FENTANILO EN DOSIS ALTAS

Un estudio con pacientes sometidos a cirujia cardiaca

SUMARIO

Se estudiaron en 20 pacientes las respuestas hormonales a la anestesia y cirujia. Diez de los pacientes fueron anestesiados con 60 µg kg^{-1} de fentanilo y óxido nitroso en óxigeno y 10 con 0,3 mg kg^{-1} de etomidato y óxido nitroso en oxigeno más halotano. No hubo cambios significativos en las concentraciones de cortisol, crecimiento hormonal o de insulina, como respuesta a operaciones quirúrjicas en cualquiera de los grupos, aunque las concentraciones de cortisol disminuyeron durante el desvio cardiovascular. Ambos grupos mostraron un incremento en las concentraciones de prolactina. Los pacientes anestesiados con etomidato y halotano, mostraron un incremento significativo en las concentraciones de adrenalina y de glucosa que no se presentaron en el grupo de fentanilo. El desvio cardiovascular se asoció; en ambos grupos, con un marcado incremento de catecolaminas.

Br. J. Anaesth. (1981), 53, 949

PHYSIOLOGICAL CORTISOL SUBSTITUTION OF LONG-TERM STEROID-TREATED PATIENTS UNDERGOING MAJOR SURGERY

T. SYMRENG, B. E. KARLBERG, B. KÅGEDAL AND B. SCHILDT

SUMMARY

In 22 patients undergoing elective surgery, adrenal function was assessed before and on the day of surgery. Patients receiving corticosteroid therapy but with a normal cortisol response to a corticotropin stimulation test (group II, $n = 8$) were not given hydrocortisone on the day of operation. Their cortisol concentration increased in a manner similar to patients (group I, $n = 8$) who had never had corticosteroid treatment. The plasma cortisol concentrations in these two groups were less than in subjects (group III, $n = 6$) with an impaired cortisol response to corticotropin stimulation, who were given hydrocortisone 25 mg at the induction of anaesthesia followed by a continuous infusion of hydrocortisone 100 mg during the next 24 h. There were no clinical signs of circulatory insufficiency in any group. The low-dose hydrocortisone therapy regimen is sufficient for substitution of adrenal function during surgery and in the early postoperative phase. It could lead to mild oversubstitution in patients with impaired adrenal insufficiency undergoing major surgery.

Patients receiving long-term corticosteroid therapy may have suppression of adrenal function (Sampson, Winstone and Brooke, 1962) and be unable to respond physiologically to surgery or other forms of stress. As a result, supplementation with corticosteroids was suggested and various regimens proposed (Plumpton, Besser and Cole, 1969). The suggested dosages were large (varying between 300 and 600 mg of hydrocortisone per 24 h). Although effective in avoiding adrenal insufficiency such regimens were advocated empirically.

However, little thought has been given to the adverse effects of corticosteroids, such as an increased susceptibility to infection, impaired wound healing and a decrease in glucose tolerance (Dujovne and Azarnoff, 1973) during and after operation in patients undergoing major surgery.

In contrast to this empirical high-dose substitution regimen, a rational low-dose substitution was proposed by Kehlet and Binder (1973). From studies of the normal adrenocortical response the total increment of cortisol was found to be 75–150 mg per 24 h in association with major surgery (Kehlet, 1976). During the subsequent 2–3 days the cortisol production declined and returned to control in uneventful cases. Kehlet proposed a bolus of hydrocortisone 25 mg at the induction of anaesthesia followed by 100 mg as a continuous infusion for the following 24 h; this he considered sufficient to avoid adrenal insufficiency (Kehlet, 1975).

When patients receiving long-term treatment with corticosteroids undergo surgery the question of supplementation arises. However, the majority of these patients receive corticosteroid treatment not because of proven adrenocortical insufficiency, but for other reasons and their adrenocortical function may or may not be impaired as a result of that therapy.

No attempts have been made to distinguish patients with an inadequate adrenal response from those responding normally to stress and consequently requiring either low-dose substitution or no substitution at all.

The purpose of the present investigation was: (a) to differentiate patients with a normal adrenal stress response from those with an inadequate response, using a preoperative corticotropin test: (b) to measure plasma cortisol concentrations during and following major surgery in patients with a normal adrenal response without administering cortisol substitution; (c) to evaluate the low-dose substitution regimen in patients with proven adrenal insufficiency by measuring plasma cortisol concentrations during and following major surgery.

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PATIENTS AND METHODS

Patients

Twenty-two patients aged from 23 to 78 yr undergoing major surgery were studied (table I). Eight patients had not received corticosteroids previously (control group, group I). Fourteen patients (constituting groups II and III after the corticotropin test) had been treated before operation with corticosteroids for varying lengths of time (2 months–12 yr; mean 34 months). The indications for this medication varied (table II) and the daily dose range (prednisolone 5–80 mg) was considerable.

TABLE I. *Details of surgery undergone by patients in each group*

	Number of patients		
Type of surgery	Group I	Group II	Group III
Procto–colectomy	3	3	3
Gastric resection	2	1	—
Small bowel or limited large bowel resection	3	1	1
Hemi-colectomy	—	2	—
Splenectomy	—	1	1
Bilateral subtotal thyroid resection	—	—	1

TABLE II. *Indications for long-term corticosteroid medication*

	Number of patients
Crohn's disease	4
Ulcerative colitis	3
Thrombocytopaenia	2
Bronchial asthma	2
Congenital adrenogenital syndrome	1
Addison's disease	1
Rheumatoid arthritis	1
Total	14

Analytical procedures

The corticotropin stimulation test was performed in all patients at 8 a.m. after an overnight fast. After a baseline (zero time) blood sample had been taken, tetracosactid 0.25 mg (Synacthèn, Ciba) was given as a bolus injection i.v. and blood samples withdrawn at 30, 60, 90 and 120 min after the injection. The samples were centrifuged within 1 h and plasma stored at −20 °C until assayed. Plasma cortisol concentration was measured by fluorimetry (de Moor et al., 1962) and plasma aldosterone concentration by the specific radioimmunoassay of McKenzie and Clements (1974) as validated in our laboratory (Tolagen and Karlberg, 1978).

Preoperative evaluation of adrenal function. The results of the corticotropin stimulation test are summarized in table III. The subjects who had never received corticosteroid treatment (group I) had, as expected, a normal cortisol response. Of the subjects who had received corticosteroid treatment previously, eight had a peak plasma cortisol concentration greater than 500 nmol litre^{-1}. They constituted group II and were not given corticosteroid treatment during surgery. The remaining six subjects (including one with Addison's disease) had low basal cortisol concentrations and subnormal peak values. They constituted group III and were given low-dose cortisol on the day of operation.

The aldosterone response to corticotropin stimulation was also studied in a limited number of subjects in order to evaluate its sensitivity as an indicator of adrenal insufficiency (table III). All three groups had normal basal aldosterone concentrations. In groups II and III the plasma aldosterone concentration increased significantly ($P < 0.05$) following the administration of corticotropin. In group I the plasma aldosterone concentration increased but not significantly, possibly because of the small number of patients investigated in this group. There were no significant

TABLE III. *Basal and corticotropin-stimulated plasma cortisol and aldosterone concentrations before operation (mean* ± SD). *Statistical significance compared with group I:* *** P < 0.001; *n.s.=not significant*

	Cortisol (nmol litre^{-1})			Aldosterone (pmol litre^{-1})		
	n	Basal value	Peak value	*n*	Basal value	Peak value
Group I	8	418±65	1084±273	4	175±146	423±301
Group II	8	487±237 n.s.	867±229 n.s.	7	335±192 n.s.	736±317 n.s.
Group III	6	109±57***	213±102***	4	342±439 n.s.	782±532 n.s.

differences between the groups. The patient with Addison's disease had no increase at all in plasma aldosterone concentration after corticotropin.

Anaesthetic procedure

All patients were given droperidol and atropine i.m. as premedication and were anaesthetized with droperidol, fentanyl, nitrous oxide and oxygen with pancuronium. The total doses of fentanyl in the three groups were 1.2 mg ± 0.1, 1.3 mg ± 0.1 and 1.2 mg ± 0.1 respectively (mean ± SEM). Mechanical ventilation was used with a tidal volume of 10 ml per kg body weight and a frequency of 12 b.p.m. During the operation 7–10 ml of Ringer-acetate solution per kg body weight was administered per hour. Blood losses were replaced with whole blood according to routine clinical practice.

At the induction of anaesthesia the patients received hydrocortisone 25 mg (Hydrocortone phosphate, MSD) i.v. and a continuous infusion of hydrocortisone 100 mg in 10% invertose solution was commenced and continued for the following 24 h. Blood samples were withdrawn for determination of cortisol and aldosterone concentrations before, and at 0.5, 1, 2, 4, 8, 16 and 24 h after, the induction of anaesthesia.

Statistical evaluation was undertaken using Student's *t* test.

RESULTS

The changes in plasma cortisol concentration attributable to the stress of surgery are presented in figure 1. The time-courses of the changes in cortisol values were similar in groups I and II except at 4 and 8 h after induction when the cortisol concentrations in group I were slightly but significantly ($P < 0.05$) greater than in group II. As expected, the basal values were significantly lower in group III compared with the other two groups ($P < 0.001$). After cortisol had been administered (group III) the plasma cortisol concentration increased markedly. During the following 2 h it was significantly ($P < 0.01$) greater than in the other two groups. Thereafter the mean values were similar to those in the other two groups.

The moderate increase in the plasma aldosterone concentration on the day of surgery was similar in all three groups following the stress of surgery and did not differ between the groups (fig. 2). The patient with Addison's disease had no increase in plasma aldosterone concentration.

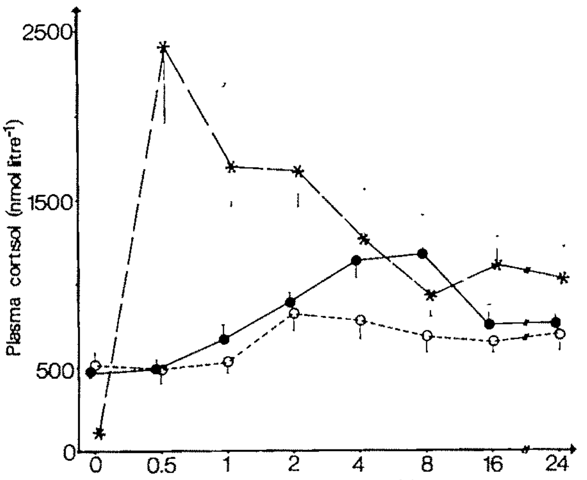

FIG. 1. Plasma cortisol response to the stress of anaesthesia and surgery. Means ± SEM. ●——● = controls; ○---○ = patients receiving long-term corticosteroid treatment with normal response to the corticotropin stimulation test (no substitution during surgery); ★---★ = patients receiving long-term corticosteroids with a subnormal response to the corticotropin test (given low-dose cortisol substitution).

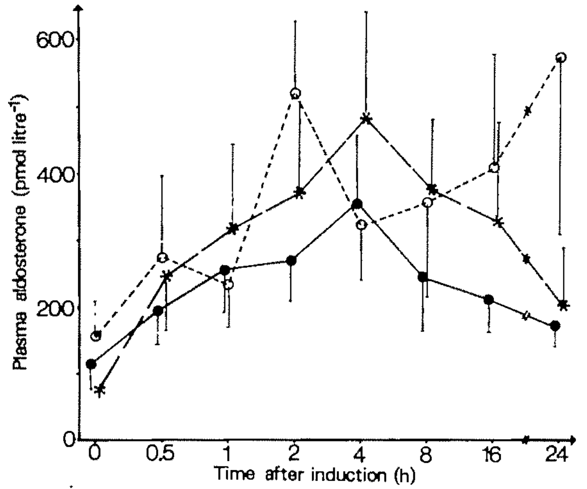

FIG. 2. Plasma aldosterone response to the stress of anaesthesia and surgery. For explanation of symbols see figure 1.

The clinical course was uneventful in all patients and there was no arterial hypotension or other sign indicating adrenal insufficiency either during surgery or after operation.

In most patients blood loss was less than 20% of the total blood volume. Mean (± SEM) estimated blood losses in the three groups were 900 ml ± 217, 1263 ml ± 259 and 833 ml ± 203 respectively. There were no statistically significant differences between the three groups in this respect. The three groups were comparable with respect to mean weight, and calculated mean blood volume.

DISCUSSION

In the 1950's deaths were reported in connection with anaesthesia and surgery among patients treated before operation with corticosteroids for varying lengths of time (Fraser, Preuss and Bigford, 1952; Lewis et al., 1953; Winstone and Brooke, 1961). Although this could not easily be explained by current knowledge, the fatal outcome was thought, among other possibilities, to be related to the long-term medication. Hypotension and shock were believed to be a result of adrenal insufficiency. Consequently, regimens were drawn up for cortisol substitution of the presumptive adrenal hypofunction (Plumpton, Besser and Cole, 1969). Although these first regimens were entirely empirical, they worked in practice and gained widespread acceptance and are in use today.

Recently, Kehlet reviewed the literature and studied those patients reported to have succumbed from supposed adrenal atrophy (Kehlet, 1976). He concluded that, in the majority, other faults in the treatment, most often inadequate replacement of blood and fluid losses, could equally have been the cause of death. In only two of 13 patients did adrenal insufficiency remain a strongly suspected cause of the fatal outcome.

An increase in the knowledge of the normal endogenous production of cortisol during conditions of stress has led subsequently to the use of a low-dose corticosteroid substitution regimen. Thus, some authors reported the cortisol response to vigorous stress, such as major surgery, to be 72–95 mg per 24 h (Hardy and Turner, 1957; Hume, Bell and Bartter, 1962). Hume, Nelson and Miller (1956) also estimated that the endogenous cortisol production was between 75 and 150 mg per 24 h in young, previously healthy, subjects with extensive burn injuries. Kehlet and Binder (1973) studied a large number of patients on previous long-term corticosteroid medication suspected of suffering from adrenal atrophy. Even when subjected to major surgery only a few of these patients were given corticosteroids because of hypotension. In addition, they observed that many of the patients were physically fit despite barely detectable plasma concentrations of cortisol.

In a later report it was found that a lumbar extradural block to the 4th thoracic segment abolished the adrenocortical response to lower abdominal surgery (Engquist et al., 1977). Despite major surgery and a blocked adrenal response, there were no clinical signs of adrenal insufficiency.

In the present study we have applied a physiological approach with regard to cortisol substitution based on an evaluation of adrenal function before operation by means of the cortisol response to corticotropin stimulation. This regimen made it possible to identify before operation those patients who had impaired adrenal function. We found that the vast majority of patients receiving long-term steroid replacement had a normal cortisol response to corticotropin stimulation. Incidentally, we had great difficulty in finding patients with suppressed adrenal function, despite investigating a large number.

The results of the corticotropin stimulation test served as a reliable basis for the prompt withdrawal of corticosteroids after surgery in patients undergoing surgery with, for example, inflammatory bowel disease and other conditions in which withdrawal of corticosteroids is desirable. This is advantageous with regard to the adverse effects of corticosteroids in connection with surgery, such as impaired wound healing, increased risk of infection, reduced glucose tolerance, electrolyte imbalance and a decrease in the duration of action of pancuronium (Dujovne and Azarnoff, 1973; Laflin, 1977).

The low-dose cortisol substitution programme used in patients with proven adrenal insufficiency indicated plasma cortisol concentrations considerably greater than the values seen in healthy controls subjected to the same degree of operative stress. Two and four hours after the induction of anaesthesia the plasma cortisol concentrations were even greater than in the control subjects.

Furthermore, the corticotropin stimulation test correctly indicated the corticosteroid-treated patients with preserved adrenal function and their response to surgery was indistinguishable from that of the control subjects (fig. 1). Therefore, it must be concluded that corticosteroid treatment during surgery with the low-dose regimen is sufficient. An increase in the dose seems unnecessary and is undesirable because of possible side-effects. Even low-dose substitution may be unnecessary in subjects receiving long-term corticosteroid treatment having a preserved endogenous cortisol release during operation. However, to deny cortisol treatment, adrenal function must be evaluated in each patient and, as this is not always possible, further decreases in the corticosteroid treatment cannot be generally recommended.

Measurement of plasma aldosterone seemed to be a far less sensitive indicator of impaired adrenal function than measurement of plasma cortisol. Moreover, the aldosterone response to corticotropin was not suppressed at all in group III as compared with group I (table III) except for the one patient with Addison's disease. There is scanty knowledge about the normal aldosterone response to corticotropin stimulation or to the stress of major surgery. Our results may indicate that aldosterone insufficiency would be rare, but this evaluation must await studies on a larger number of patients.

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SUBSTITUTION DU CORTISOL PHYSIOLOGIQUE CHEZ LES MALADES TRAITES DEPUIS LONGTEMPS A L'AIDE DES STEROIDES LORS D'UNE INTERVENTION CHIRURGICALE MAJEURE

RESUME

Sur 22 malades subissant une intervention chirurgicale à froid, on a procédé à une évaluation de la fonction surrénale la veille et le jour même de l'intervention chirurgicale. Les malades suivant un traitement corticostéroïde, mais ayant eu une réaction normale du cortisol à un test de stimulation à la corticotropine (groupe II, $n = 8$) n'ont pas reçu d'hydrocortisone le jour de l'opération. Leurs concentrations de cortisol ont augmenté d'une manière similaire à celle des patients (groups I, $n = 8$), n'ayant jamais été traités par les corticostéroïdes. Les concentrations de cortisol dans le plasma pour ces deux groupes ont été inférieures à celles constatées sur les sujets (groupe III, $n = 6$) ayant eu une réaction affaiblie à la stimulation par la corticotrophine, malades auxquels on avait administré 25 mg d'hydrocortisone au commencement de l'anesthésie, suivis par une perfusion d'hydrocortisone—100 mg au cours des 24 heures suivantes. Il n'y a eu de signes cliniques d'insuffisance circulatoire dans aucun des groupes. Le traitement par un régime d'hydrocortisone à faible dose est suffisant pour qu'il se produise une substitution de la fonction surrénale pendant l'intervention chirurgicale et au cours de la phase postopératoire primaire. Cela peut entraîner une légère sursubstitution chez les malades souffrant d'une insuffisance surrénale et subissant une intervention chirurgicale majeure.

PHYSIOLOGISCHER CORTISOL-ERSATZ BEI LANGFRISTIG MIT STEROIDEN BEHANDELTEN PATIENTEN BEI GROSSANGELEGTEN OPERATIONEN

ZUSAMMENFASSUNG

Bei 22 Operationspatienten wurde die Nebennierenfunktion vor und am Tage der Operation untersucht. Patienten unter Kortikosteroid-Therapie, aber mit normaler Cortisol-Reaktion auf einen Kortikotropin-Stimulationstest (Gruppe

II, $n = 8$) erhielten am Operationstag kein Hydrocortison. Ihre Cortisol-Konzentration stieg auf ähnliche Weise wie bei den Patienten (Gruppe I, $n = 8$), die nie eine Kortikosteroid-Behandlung erhalten hatten. Die Cortisolkonzentrationen in diesen beiden Gruppen waren geringer als bei den Patienten (Gruppe III, $n = 6$), deren Cortisol-Reaktion auf Kortikotropin beeinträchtigt war und die Hydrocortison 25 mg bei Narkosebeginn erhielten, gefolgt von einer kontinuierlichen Infusion von Hydrocortison 100 mg über die nächsten 24 Stunden. In keiner der drei Gruppen gab es klinische Anzeichen einer Kreislaufinsuffizienz. Die niedrig dosierte Hydrocortison-Behandlung ist ausreichend für den Ersatz der Nebennierenfunktion während des Eingriffs, sowie in der ersten postoperativen Phase. Sie könnte bei Patienten mit beeinträchtigter Nebennierenfunktion bei grossen Operationen zu einer milden Übersubstitution führen.

SUSTITUCION FISIOLOGICA DE CORTISOL EN PACIENTES QUE HAN RECIBIDO UN PROLONGADO TRATAMIENTO DE ESTEROIDES Y QUE ESTAN SOMETIDOS A OPERACION QUIRURJICA MAYOR

SUMARIO

Se evaluó la función adrenal en el día de la operación de 22 pacientes sometidos a operación quirúrjica facultativa y después de dicha operación. A los pacientes bajo terapia de corticosteroides pero con una respuesta de cortisol normal ante una prueba de corticotropin de estimulación (grupo II, $n = 8$), no se les administró hidrocortisona el día de la operación. Su concentración de cortisol incrementó de modo similar a la de los pacientes (grupo I, $n = 8$) que no habían recibido nunca tratamiento de corticosteroides. Las concentraciones de cortisol en estos grupos fueron inferiores a las de los sujetos (grupo III, $n = 6$) que presentaban una respuesta de cortisol anormal ante la estimulación de corticotropin y a los que se les administraron 25 mg de hidrocortisona durante la inducción de la anestesia, seguidos de una infusión continua de 100 mg de hidrocortisona durante las 24 horas siguientes. No se presentaron signos de insuficiencia circulatoria en ninguno de los grupos. El régimen terapéutico de baja dosis de hidrocortisona es suficiente para sustituir la función adrenal durante la operación quirúrjica y en la fase posoperativa inicial. Podria llevar a una sobresustitución moderada en aquellos pacientes que presenten una insuficiencia adrenal anormal y que estén sometidos a una operación quirúrjica de importancia.

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SUXAMETHONIUM-INDUCED CHANGES IN SERUM CREATINE PHOSPHOKINASE

D. S. CHARAK AND C. L. DHAR

SUMMARY

In sixty patients undergoing minor surgical procedures with minimal involvement of muscle, there was a significant increase in serum creatine phosphokinase induced by suxamethonium. The increase was significantly reduced by prior administration of tubocurarine 3 mg and by pretreatment with suxamethonium 10 mg.

Tammisto and Airaksinen (1966) reported increased creatine phosphokinase activity after suxamethonium, edrophonium and neostigmine. The increase was reported to be influenced by the induction agent (Tammisto and Airaksinen, 1966; Tammisto, Leikkonen and Airaksinen, 1967) and by pretreatment with a small dose of tubocurarine (Tammisto, Leikkonen and Airaksinen, 1967).

We measured the increase in serum creatine phosphokinase activity induced by suxamethonium given after thiopentone and the effect of pretreatment with a small dose of either tubocurarine or suxamethonium.

PATIENTS AND METHODS

Sixty young healthy adults of either sex undergoing minor surgical procedures with minimal muscle involvement were studied in three groups of 20. They were prepared for surgery by 6 h fasting before operation; atropine 0.6 mg was given i.m. 45–60 min before induction of anaesthesia.

Group I. Induction with thiopentone 5 mg kg^{-1} i.v. immediately followed by suxamethonium chloride 1 mg kg^{-1} i.v.

Group II. Tubocurarine 3 mg followed after 3 min by thiopentone and suxamethonium as in group I.

Group III. Induction with thiopentone 5 mg kg^{-1} i.v. followed by suxamethonium 10 mg i.v., followed after 45–60 s by a full relaxant dose (1 mg kg^{-1}) of the drug.

In all the three groups patients were observed for the appearance of muscle fasciculations which were graded as 0, 1, 2 and 3 (Cullen, 1971).

Venous blood was collected in plastic centrifuge tubes for estimation of serum creatine phosphokinase. The first sample was collected just before induction and another 24–28 h after anaesthesia. The plastic tubes were allowed to stand at room temperature for 30 min. After centrifugation for 15 min clear serum was obtained. Creatine phosphokinase was assayed by the method described by Kuby, Noda and Lardy (1954), determining the acid-labile phosphorus by the method of Fiske and Subbarow (1925). The chemicals used were: creatine, ATP, cysteine hydrochloride, Tris buffer and magnesium chloride. The CPK activity was expressed in mg of phosphorus liberated per litre of serum per hour of incubation.

RESULTS

CPK values before operation varied between 0 and 45 units (mean 25 ± 3.5) (table I).

Mean CPK before operation in group I was 25.36 ± 13.3; in group II 24.87 ± 13.99 and in group III 25.71 ± 11.59. The variation in CPK values before operation in different groups and grades was not statistically significant. Compared with group I the mean values after operation in groups II and III were significantly less; t test: $P < 0.001$ and $P < 0.005$ respectively. The differences after operation between group II and III were not statistically significant. CPK changes were related to grade of fasciculation and there was found to be a significant positive correlation between the severity of change and the grade of fasciculation ($P < 0.01$) for all groups.

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TABLE I. *Grade of fasciculation and creatine phosphokinase (CPK) values in serum*

Grade of fasciculation		No. patients	Mean CPK (mg P litre^{-1} h^{-1}) Before operation	After operation	Mean increase
Group I	0	1	23.50	23.50	0
	I	6	28.80 ± 14.13	63.50 ± 14.24	34.7
	II	9	26.70 ± 14.85	76.80 ± 17.32	50.1
	III	4	19.20 ± 11.61	99.30 ± 14.28	80.1
Total		20	25.36 ± 13.3	75.85 ± 22.92	50.49
Group II	0	4	26.75 ± 22.4	33.12 ± 26.1	6.35
	I	13	25.80 ± 12.83	50.98 ± 16.47	25.18
	II	3	17.83 ± 4.4	68.00 ± 14.72	50.17
	III	—	—	—	—
Total		20	24.87 ± 13.99	49.96 ± 20.36	25.09
Group III	0	3	29.76 ± 8.97	34.00 ± 8.28	4.24
	I	12	27.60 ± 12.15	59.49 ± 15.69	31.89
	II	4	23.57 ± 7.6	79.97 ± 7.43	56.46
	III	1	0	76.50	76.50
Total		20	25.71 ± 11.59	60.61 ± 21.92	34.90

DISCUSSION

The results of this study confirm those of Airaksinen and Tammisto (1966), Tammisto and Airaksinen (1966) and Tammisto and others (1970). Suxamethonium induces an increase in serum CPK activity as a result of leakage of the enzyme, probably caused by the process of depolarization. Pretreatment with tubocurarine 3 mg 3 min before administration of suxamethonium resulted in a smaller increase after operation. This confirms the findings of Tammisto, Leikkonen and Airaksinen (1967). Pretreatment with suxamethonium 10 mg itself is known to reduce the severity of fasciculations (Baraka, 1977) and the present study confirms this.

Our finding of a significant correlation between the degree of change in CPK and the grade of fasciculation is in agreement with the assumption of Tammisto and Airaksinen (1966) that the strain caused by the fasciculations seemed to be the cause of the efflux of CPK from the muscle cell and, in certain cases of severe fasciculation, myoglobin (Bennike and Jarnum, 1964; Tammisto and Airaksinen, 1965; Ryan, Kagen and Hyman, 1971). Other factors like anoxia, lack of glucose and cooling (interfering with energy production), abnormalities in carbohydrate metabolism, efflux of potassium itself and abnormalities of thyroid function have also been incriminated as causative factors in the release of CPK from muscle cells induced by suxamethonium (Tammisto, Leikkonen and Airaksinen, 1967).

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ALTERATIONS DE LA PHOSPHOKINASE DE CREATINE DU SERUM PROVOQUEES PAR LE SUXAMETHONIUM

RESUME

On a constaté chez soixante patients soumis à des opérations chirurgicales mineures comportant des complications musculaires minimales une augmentation significative de la phosphokinase de créatine du sérum causée par le suxaméthonium. Cette augmentation a été sensiblement réduite par l'administration préalable de 3 mg de tubocurarine et un pré-traitement avec 10 mg de suxaméthonium.

DURCH SUXAMETHONIUM BEWIRKTE ÄNDERUNGEN IN DER SERUMKREATINPHOSPHOKINASE

ZUSAMMENFASSUNG

Bei 60 Patienten mit kleinen chirurgischen Eingriffen bei minimalen Muskelsektionen wurde durch Suxamethonium ein wesentlicher Anstieg an Serum-Kreatinphosphokinase bewirkt. Dieser wurde wesentlich reduziert durch vorherige Verabreichung von Tubocurarin 3 mg und durch Vorbehandlung mit 10 mg Suxamethonium.

ALTERACIONES DE LA FOSFOQUINASA CREATINA DEL SUERO INDUCIDAS POR EL SUXAMETONIO

SUMARIO

En sesenta pacientes sometidos a operaciones quirúrgicas menores con complicación muscular mínima, hubo un aumento significativo de la fosfoquinasa creatina en el suero inducido por el suxametonio. Este aumento se redujo de manera significativa mediante administración previa de 3 mg de tubocurarina y por pre-tratamiento con 10 mg de suxametonio.

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ETOMIDATE AND FENTANYL FOR MAINTENANCE OF ANAESTHESIA

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SUMMARY

An infusion of etomidate and fentanyl was compared with halothane or morphine plus nitrous oxide in oxygen for the maintenance of anaesthesia in 200 patients. Cardiovascular and respiratory changes were found to be similar in the two groups. There was a prolongation of recovery time in the etomidate-fentanyl group: this was possibly a result of lack of flexibility in the infusion technique.

Etomidate can be used as an anaesthetic induction agent (Miller, Hendry and Lees, 1978). In this role its major disadvantages are pain on injection and excitatory movements. In the present study etomidate was combined with fentanyl and used, as an infusion, to maintain anaesthesia. This technique was compared with a conventional technique using halothane, or morphine, with nitrous oxide in oxygen.

PATIENTS AND METHODS

Two hundred patients undergoing general surgical or gynaecological operations were allocated to two groups of 100 patients matched for age, sex, weight, body build and operative procedure (tables I, II).

TABLE I. *Clinical details of patients and duration of operations. Mean values; SEM in parentheses*

	Sex	Respiratory mode	Age (yr)	Weight (kg)	Duration (min)
Group A	19M 31F	IPPV ($n = 50$)	55 (3)	60 (3)	92 (8)
	21M 29F	Spont. ($n = 50$)	47 (3)	64 (2)	35 (3)
Group B	19M 31F	IPPV ($n = 50$)	56 (3)	60 (3)	87 (5)
	21M 29F	Spont. ($n = 50$)	47 (3)	64 (1)	43 (5)

After premedication with a narcotic analgesic and atropine or hyoscine, anaesthesia was induced with thiopentone 6 mg kg^{-1} and fentanyl 1.2 µg kg^{-1}. When necessary, the trachea was intubated following suxamethonium 100 mg. Tubocurarine 0.5 mg kg^{-1} was given when prolonged neuromuscular blockade was required and the lungs were ventilated artificially.

TABLE II. *Types of surgery in the two groups (matched pairs)*

	No. pairs
IPPV	
Upper abdomen	14
Lower abdomen	16
Major gynaecological	15
Peripheral vascular	5
Total	50
Spontaneous ventilation	
Mastectomy and biopsy	15
Inguinal hernia, hydrocoele etc.	10
Haemorrhoidectomy	7
Minor gynaecological	11
Varicose vein	5
Head and neck	2
Total	50

The infusion group (A) breathed 40% oxygen in nitrogen. Anaesthesia was maintained with an i.v. infusion of etomidate and fentanyl in normal saline (etomidate 2.5 mg ml^{-1} and fentanyl 7 µg ml^{-1}) given from a Treonic DC2 rotary pump. Following a rapid initial infusion (3–4 ml min^{-1} for 2–3 min) the rate of infusion was decreased according to the patient's response to surgical stimulation as judged by changes in heart rate, arterial pressure, sweating, lachrymation and, in those who were breathing spontaneously, respiratory rate. The mean total doses (± SEM)

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were etomidate $20 \pm 1.6\,\mu g\,kg^{-1}\,min^{-1}$ and fentanyl $0.053 \pm 0.0045\,\mu g\,kg^{-1}\,min^{-1}$.

The control group (B) breathed 33% oxygen in nitrous oxide supplemented with halothane during spontaneous ventilation or morphine $0.2\,mg\,kg^{-1}$ during artificial ventilation. Physiological saline solution was infused i.v. at a rate similar to the rate of fluid administration in group A.

In all patients heart rate, arterial pressure (oscillotonometer) and e.c.g. were monitored. In 20 spontaneously breathing patients from each group arterial blood was sampled before the induction of anaesthesia, 20 min after a steady state of maintenance anaesthesia has been achieved and 15 min after the end of operation. Blood-gas tensions were measured using an ABL1 Automatic Gas Analyser.

The time from the end of anaesthesia until the patient obeyed simple commands was noted by the recovery room staff, who were unaware of the method of anaesthesia. The time of the first administration of analgesia after operation was recorded. All patients were visited on the day after surgery and the infusion site inspected for evidence of damage to veins.

Student's *t* test was used to analyse the cardiovascular, respiratory and recovery data. χ^2 test was used to compare the amounts of analgesia given, and the frequency of venous sequelae.

RESULTS

Quality of anaesthesia

No problems were encountered during anaesthesia in any of the patients receiving artificial ventilation. The maintenance of anaesthesia was unsatisfactory in three men (group A) who were breathing spontaneously and undergoing haemorrhoidectomy. However, there was difficulty also in obtaining a sufficiently deep level of anaesthesia during the maintenance period in two fit young men in group B undergoing the same operation. On no occasion was the chosen method of anaesthesia abandoned.

Time to recovery

Recovery time in group B was shorter (12.5 ± 1.8 (SEM) min) than in group A (15.8 ± 2.3 (SEM) min). This difference was not significant. In group A 12% of patients receiving IPPV and 25% of those breathing spontaneously had not recovered consciousness within 40 min. Wakening could be produced readily by the injection of naloxone 0.1–0.2 mg i.v. Restlessness occurred in six patients who received an injection of morphine i.m.

Respiration

In patients in whom blood-gas tensions were measured the percentage changes in the mean arterial carbon dioxide tensions in group B were significantly ($P < 0.02$) greater than those from group A during surgery but were comparable 15 min after the end of anaesthesia (table III).

TABLE III. *Effect of anaesthesia on mean* Pa_{CO_2} *in spontaneously breathing patients. Values are expressed as percentage change from values before operation* (± *SEM*). *$P < 0.02$ *group A compared with group B*

	Percentage increase (± SEM)	
	During anaesthesia	15 min after op.
Group A	9.8 (± 1.1*)	8.1 (± 1.4)
Group B	14.6 (± 1.9*)	8.0 (± 1.7)

Circulation

Compared with the values before operation no clinically significant changes in mean heart rate or arterial pressure were noted in either group. Group B (halothane) showed significant decreases in systolic and diastolic pressures and heart rate after induction. The values remained significantly ($P < 0.05$) lower throughout the operation, except for the systolic pressure, which was not significantly different from group A during the maintenance of anaesthesia.

Nausea and vomiting

Four patients in group A, all of whom had received naloxone, complained of nausea and vomiting, compared with six in group B, four of whom had received morphine anaesthesia.

Postoperative analgesia

There was no significant difference between the groups in the time until the first injection of analgesic: the mean time in group A was 6.8 ± 1.0 (SEM) h compared with 6.4 ± 0.8 (SEM) h in group B. On direct questioning, no patient had recall of any event after insertion of the "Butterfly" needle until awakening in the ward.

Venous sequelae

Thrombosis of the infused vein occurred in 15 patients being ventilated artificially in group A, compared with seven patients breathing spontaneously. In the majority of the 15 patients

2.5–5 cm of the vein was hard, and there was neither tenderness nor inflammation. However in six patients a more extensive thrombophlebitis was observed. In group B, six patients being ventilated artificially and four breathing spontaneously had evidence of venous thrombosis.

DISCUSSION

The infusion of etomidate and fentanyl produced satisfactory maintenance of anaesthesia in most patients. Irrespective of the mode of ventilation, cardiovascular stability was comparable to that obtained in the artificially ventilated patients in group B and superior to that in the patients in group B receiving halothane. Mean Pa_{CO_2} was lower in the infusion group compared with the halothane group.

The venous sequelae may have been related to the longer duration of infusion into relatively small veins. Our previous experience (unpublished) of infusion via a fast-running i.v. infusion caused a much lower frequency of venous sequelae.

T. M. O'Carroll (personal communication) using a maintenance dose of etomidate $42 \mu g kg^{-1} min^{-1}$ and fentanyl $0.033 \mu g kg^{-1} min^{-1}$ found an increase in muscle movement and muscle tone during anaesthesia. Since muscle movement is a feature of etomidate infusion without fentanyl (Kay and Rolly, 1977), and as it was conspicuously absent in this series, it may be that lower doses of etomidate and larger doses of fentanyl give better conditions.

The combination of thiopentone as an induction agent and an etomidate–fentanyl infusion to maintain anaesthesia provides a practical, pollution-free anaesthetic technique with satisfactory conditions for patient and surgeon. However, the use of a fixed ratio of the two drugs, although satisfactory for the majority of patients, does not allow titration of analgesia and hypnosis in the individual patient. Further studies are required to determine the optimal dosage scheme.

ACKNOWLEDGEMENTS

We thank Janssen Pharmaceuticals for the gift of the concentrated form of etomidate used, and also for their encouragement; the surgeons at the Victoria Infirmary, Glasgow for their help in this project; and Dr W. S. Nimmo for helpful advice in the preparation of this manuscript.

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ETOMIDATE ET FENTANYL POUR MAINTENIR L'ANESTHESIE

RESUME

On compara une infusion d'étomidate et de fentanyl avec de l'halothane ou de la morphine avec du protoxyde d'azote dans de l'oxygéne aux fins du maintien de l'anesthésie, chez 200 patients. Les changements cardiovasculaires et respiratoires s'avérèrent analogues chez les deux groupes. Il y eut une prolongation de la période de récupération dans le groupe à l'etomidate–fentanyl: c'est peut-être là le résultat du manque de flexibilité de la technique d'infusion.

ETOMIDAT UND FENTANYL ZUR AUFRECHTERHALTUNG DER NARKOSE

ZUSAMMENFASSUNG

Eine Infusion von Etomidat und Fentanyl wurde mit Halothan oder Morphium mit Stickoxyd in Sauerstoff als Methode zur Aufrechterhaltung der Narkose bei 200 Patienten verglichen. Kardiovaskuläre und respiratorische Veränderungen waren in beiden Gruppen ähnlich. Die Erholungszeit dauerte in der Etomidat/Fentanyl-Gruppe länger: möglicherweise aufgrund mangelhafter Flexibilität der Infusionsmethode.

EL ETOMIDATO Y EL FENTANILO PARA LA MANTENCIÓN DE LA ANESTESIA

SUMARIO

Se procedió a la comparación, con el propósito de mantener la anestesia en 200 pacientes, de una infusión de etomidato y fentanilo con halotano y morfina con óxido nitroso. Se comprobó que los cambios cardiovasculares y respiratorios eran similares en los dos grupos. Hubo una prolongación del tiempo de recuperación en el grupo etomidato–fentanilo: es posible que esto resultase de la falta de flexibilidad en la técnica de infusión.

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PROBLEMS IN ANAESTHESIA FOR HUGE THYROID GOITRES

V. N. SWADIA, N. D. SWADIA AND S. S. SABNIS

SUMMARY

The anaesthetic management of 12 patients with very large thyroid goitres is described. The main problems relate to abnormalities of the trachea and substantial operative blood loss.

Endemic goitre is commonly found throughout the mountainous Baroda district of Gujarat, India. This region is mainly inhabited by illiterate, tribal people who frequently present late with large goitres. An example of a "goitre family" is shown in figure 1. We present our recent experience of the management of anaesthesia for removal of this goitre.

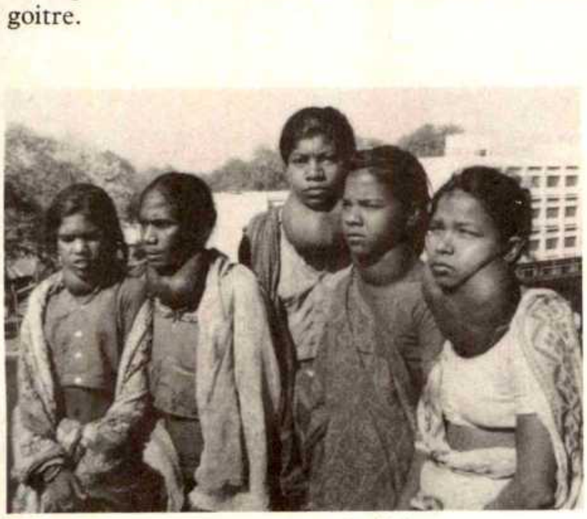

FIG. 1. A "goitre family".

PATIENTS

Two men and 10 women aged 18–43 yr were anaesthetized for removal of goitre over a 2-yr period. Before operation three patients gave a history of voice change; all the patients denied experiencing dyspnoea on exertion or on change of posture. The neck circumference of the patients averaged approximately 60 cm (range 47–80 cm) (fig. 2). None had clinical evidence of thyrotoxicosis or of retrosternal extension of the goitre. Direct laryngoscopy with topical anaesthesia revealed that five patients had restriction of movement of the vocal cords; one had bilateral adduction of the cords. Anteroposterior and lateral x-radiographs of the neck were taken to delineate the degree of compression, deviation and lengthening of the trachea (fig. 3).

ANAESTHETIC TECHNIQUE

The patients were premedicated with a mixture of either morphine or pethidine and promethazine. Anaesthesia was induced with thiopentone and, when it was ascertained that ventilation of the lungs could be assisted easily, suxamethonium was given to facilitate orotracheal intubation with a cuffed latex Magill tube. Any respiratory obstruction resulting from pressure on the trachea at the time of induction was relieved by lifting the goitre anteriorly. Anaesthesia was maintained by controlled ventilation with nitrous oxide in oxygen delivered from a Bain circuit. Tubocurarine was used as the neuromuscular blocker.

Operative blood loss was substantial, being almost one-half the estimated blood volume of the patient. Total operating time was 3–6.5 h.

After the enlarged thyroid had been removed, the endotracheal tube was partially withdrawn and the trachea examined, as described by Singh, Rao and Prasanna (1978). Detection of tracheomalacia proved difficult and therefore in nine patients the tube was left in place for 12–24 h after operation to ensure that tracheal collapse did not occur.

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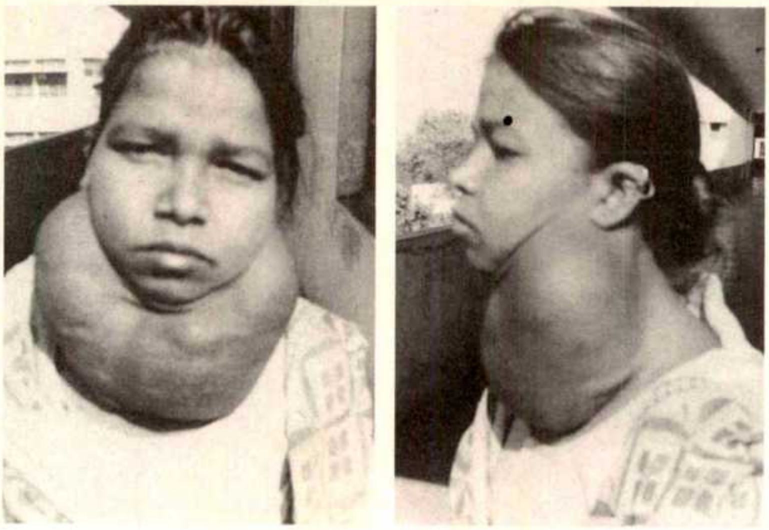

FIG. 2. Example to show size of goitre.

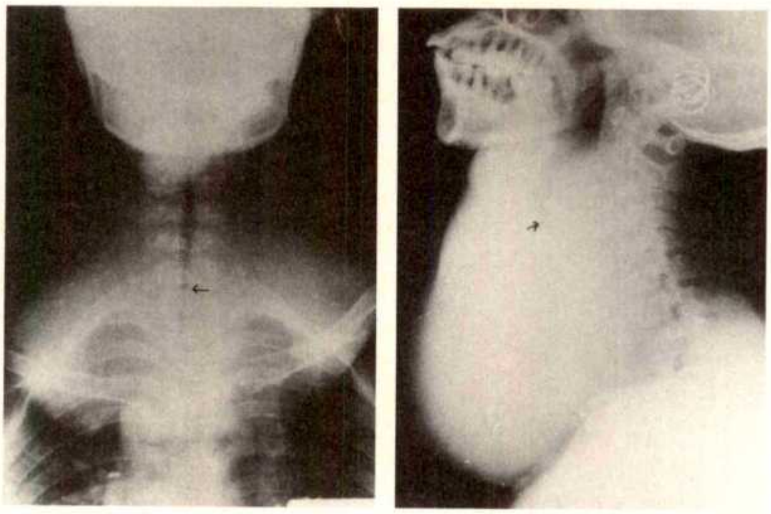

FIG. 3. AP and lateral x-radiographs. Arrows indicate deviation and narrowing of the trachea.

DISCUSSION

The surgical features of removal of giant goitres have been reviewed by Olurin (1971) and aspects of the anaesthetic management have been discussed by Singh, Rao and Prasanna (1978) and Howells (1979).

In the present series no difficulties were encountered in viewing and intubating the larynx, unlike the case report of Singh, Rao and Prasanna (1978). A likely source of difficulty is in the passage of an endotracheal tube along a deviated and possibly compressed trachea; for this the use of a new latex Magill tube is recommended. Postoperative collapse of the trachea as a result of tracheomalacia or to kinking of a lengthened trachea (Olurin, 1971) can be avoided by leaving the endotracheal tube in place.

The principal problem encountered in the present series was a consistently high blood loss, as also occurred in the case described by Singh, Rao and Prasanna (1978). It is therefore recommended that an excessive blood loss is anticipated and that an adequate volume of cross-matched blood is available.

ACKNOWLEDGEMENT

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PROBLEMES D'ANESTHESIE AVEC LES TRES GROS GOITRES DE LA THYROIDE

RESUME

Nous décrivons dans cet article la conduite de l'anesthésie effectuée sur 12 patients ayant de très gros goitres de la thyroïde. Les principaux problèmes rencontrés se rapportent aux anomalies de la trachée et à une perte de sang importante pendant l'opération.

ANÄSTHESIEPROBLEME BEI ABNORM GROSSEN KRÖPFEN

ZUSAMMENFASSUNG

Die Anästhesiebehandlung von 12 Patienten mit abnorm grossen Kröpfen wird beschrieben. Die Hauptprobleme beziehen sich auf Abnormalitäten der Trachea und erheblichen operativen Blutverlust.

PROBLEMAS EN LA ANESTESIA DE PACIENTES CON BOCIOS DE GRANDES DIMENSIONES EN LA TIROIDES

SUMARIO

Se describe la gestión de la anestesia de 12 pacientes con bocios de grandes dimensiones en la tiroides. Los problemas principales se relacionaron a las anormalidades de la traquea y a la pérdida sustancial de sangre durante la operación.

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INTRAOCULAR AND INTRACRANIAL PRESSURE DURING RESPIRATORY ALKALOSIS AND ACIDOSIS

R. B. SMITH, A. A. AASS AND E. M. NEMOTO

SUMMARY

Intraocular and intracranial pressures (IOP and ICP) were measured at four different arterial carbon dioxide tensions by direct continuous techniques in Rhesus monkeys during anaesthesia with halothane and nitrous oxide. Increases in IOP correlated significantly with Pa_{CO_2} ranging from 2.66 to 10.24 kPa ($P < 0.001$). Increases in ICP correlated significantly ($P < 0.001$) with Pa_{CO_2} between 2.66 and 7.71 kPa, but plateaued thereafter. When Pa_{CO_2} was decreased rapidly, Pa_{CO_2}, IOP and ICP decreased exponentially with similar half-times. The fast changes in IOP and ICP can probably be explained by an alteration of intraocular and intracranial blood volumes. IOP usually remained within the normal range, even at maximum Pa_{CO_2}.

Intraocular pressure (IOP) is determined by the rates of formation and outflow of aqueous humour, the volume of intraocular vessels and extraocular compressive forces. During general anaesthesia, surgical and pharmacological factors may alter IOP by direct action on the eye or indirectly through changes in circulation and respiration. A detailed discussion was presented in a recent symposium on Anaesthesia and the Eye (Spence and Norman, 1980). Respiration can effect IOP by altering Pa_{CO_2} and by influencing intrathoracic and central venous pressures. Duncalf and Weitzner (1963) recorded anterior chamber pressure of dogs and found that IOP increased by an average of 35.2% when mean Pa_{CO_2} was increased by 3.33 kPa following inhalation of carbon dioxide. Hyperventilation reduced IOP in three of four experiments as Pa_{CO_2} decreased. The eyes of higher mammals receive their blood mainly from the internal carotid artery, while in the dog the eye is supplied from both the external and the internal carotid arteries (Wolff and Last, 1968). This may invalidate extrapolation of findings in the dog to man, but similar results have been reported in man (Adams and Barnett, 1966; Meyer and Opitz, 1970; Samuel and Beuagie, 1974; Kaufmann, 1975) using indirect and intermittent measurements of IOP.

This study investigated the relationship between IOP and Pa_{CO_2} by direct and continuous IOP measurements in Rhesus monkeys during anaesthesia to obtain results of clinical significance to man. Intracranial pressure (ICP) was measured continuously for comparison with IOP.

METHODS

Nine Rhesus monkeys, weights 2.5–3.5 kg, were anaesthetized with 4% halothane in oxygen. The trachea was intubated (tubes 3–5 mm i.d.) and anaesthesia maintained with 0.5% halothane and 50% nitrous oxide. A peripheral vein was cannulated and 5% dextrose and 0.45% sodium chloride solution infused at a rate of $5\,\text{ml}\,\text{kg}^{-1}\,\text{h}^{-1}$. Pancuronium $0.2\,\text{mg}\,\text{kg}^{-1}$ was administered i.v. as required for muscle relaxation and ventilation of the lungs controlled with a Harvard fixed volume ventilator. End-tidal carbon dioxide was monitored continuously with a Godart Capnograph and maintained initially between 4 and 6%. A transurethral catheter was placed in the bladder and a metal probe inserted for continuous recording of temperature which was maintained between 37 and 39 °C with a warming blanket or lamp. Catheters for central venous and arterial pressure recordings and blood sampling were inserted to the femoral vessels. ICP was monitored via a multiple-hole silastic catheter inserted subdurally

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over the parietal cortex and secured with Eastman 910 cement. The anterior chamber of one eye was punctured with a fluid filled 25-gauge needle, care being taken to prevent loss of aqueous humour. IOP, ICP, mean arterial pressure (m.a.p.), heart rate (HR) and central venous pressure (c.v.p.) were measured with strain gauges and recorded continuously.

IOP, ICP, m.a.p., c.v.p., HR and arterial pH and gas tensions were determined at four arterial tensions of carbon dioxide. The ventilation rate and tidal volume were first adjusted to set Pa_{CO_2} at about 2.66 kPa. Normocarbia, moderate hypercarbia, and marked hypercarbia were then produced by adding carbon dioxide to the inhaled gases. Ten minutes or more was allowed for equilibration at each step before recordings were made. Carbon dioxide inhalation was chosen in preference to hypoventilation as the different conditions required for study occurred more rapidly (Nunn, 1975) and changes in intrathoracic pressure were avoided. The experiment was repeated in a few of the animals.

IOP and ICP were then studied under conditions of varying Pa_{CO_2} to establish the time relationship between them. Hypercarbia was produced first and the inhaled carbon dioxide was turned off. IOP, ICP and Pa_{CO_2} were then measured at 0, 1, 2, 3, 4, 5, 6, 8 and 10 min.

F-test was used for determination of significance of linear correlations and Student's *t* test for comparison of mean values.

RESULTS

IOP and ICP at four arterial tensions of carbon dioxide

A statistically significant direct correlation was found between the mean values of IOP and Pa_{CO_2} ($P<0.001$) (table I, fig. 1). Although mean ICP correlated significantly ($P<0.001$) with mean Pa_{CO_2} between 2.66 and 7.71 kPa, thereafter it did not increase with increasing Pa_{CO_2} (table I, fig. 2).

Table II shows average increases in IOP per unit increase in Pa_{CO_2} to be similar at different tensions of carbon dioxide. In contrast, changes in ICP were significantly greater when Pa_{CO_2} was increased from 2.66 to 5.05 kPa ($P<0.01$) and 5.05 to 7.71 kPa ($P<0.02$) than when Pa_{CO_2} was increased from 7.71 to 10.24 kPa (table II).

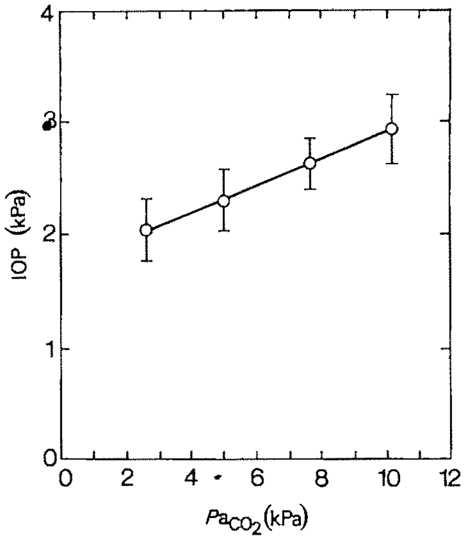

FIG. 1. Variation in IOP with Pa_{CO_2}.

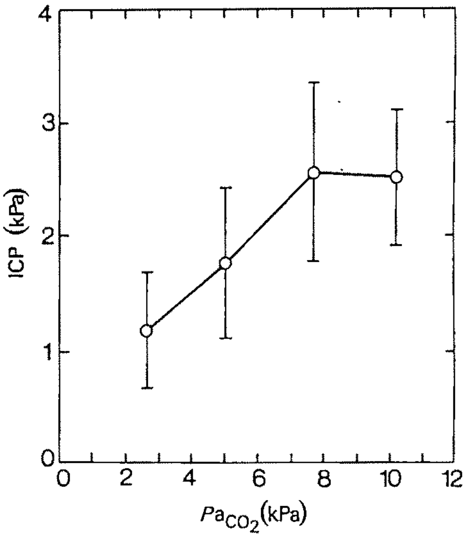

FIG. 2. Variation in ICP with Pa_{CO_2}.

Changes in c.v.p., HR and Pa_{O_2} were insignificant. However, m.a.p. decreased significantly ($P<0.05$) from a mean of 94 (SD 13) mmHg to 82 (SD 15) mmHg as Pa_{CO_2} was increased from normal to 10.24 kPa.

IOP and ICP during rapid change of Pa_{CO_2}

There were seven experiments in which Pa_{CO_2} was allowed to decrease rapidly (figs 3, 4). After a

TABLE I. *Intraocular and intracranial pressures at four different arterial tensions of carbon dioxide. n.s. = not significant*

Experiment	Pressure (kPa)	Pa_{CO_2}				Correlation with Pa_{CO_2}
		I	II	III	IV	
1	Pa_{CO_2}	2.26	4.79	7.58	9.97	
	IOP	2.13	2.26	2.79	3.59	$P<0.05$
	ICP	0.80	1.33	2.33	2.46	$P<0.05$
2	Pa_{CO_2}	2.66	4.26	6.78	8.50	
	IOP	1.86	1.99	2.53	3.19	$P<0.05$
	ICP	0.86	1.20	2.79	3.06	$P<0.05$
3	Pa_{CO_2}	2.13	4.92	7.18	10.37	
	IOP	1.79	2.39	2.79	3.06	$P<0.05$
	ICP	0.80	1.46	2.59	2.59	n.s.
4	Pa_{CO_2}	2.39	4.92	6.78	10.24	
	IOP	1.66	1.99	2.33	2.53	$P<0.05$
	ICP	0.27	0.66	1.20	1.46	$P<0.05$
5	Pa_{CO_2}	2.93	5.19	7.30	9.84	
	IOP	2.39	2.66	2.79	2.79	n.s.
	ICP	1.60	1.86	1.46	1.46	n.s.
6	Pa_{CO_2}	2.39	5.32	8.78	10.51	
	IOP	2.13	2.46	2.79	3.19	$P<0.05$
	ICP	1.53	1.86	3.72	2.66	n.s.
7	Pa_{CO_2}	3.59	5.19	9.31	10.90	
	IOP	2.39	2.66	2.86	3.06	$P<0.05$
	ICP	8.64	1.60	2.66	2.79	$P<0.05$
8	Pa_{CO_2}	2.79	3.99	6.65	10.64	
	IOP	1.86	2.13	2.53	2.86	$P<0.05$
	ICP	0.93	1.46	2.59	2.66	n.s.
9	Pa_{CO_2}	3.86	6.65	7.58	8.91	
	IOP	2.26	2.39	2.53	2.79	n.s.
	ICP	1.60	2.66	2.39	2.53	n.s.
10	Pa_{CO_2}	2.93	6.78	9.31	11.84	
	IOP	2.33	2.66	2.86	2.79	$P<0.05$
	ICP	1.53	2.86	2.86	2.79	n.s.
11	Pa_{CO_2}	3.19	4.78	8.38	10.77	
	IOP	1.93	1.99	2.46	2.79	$P<0.01$
	ICP	2.13	2.66	3.99	3.59	n.s.
12	Pa_{CO_2}	1.86	4.39	7.46	11.04	
	IOP	1.60	1.99	2.19	2.46	$P<0.05$
	ICP	1.06	1.60	2.13	2.26	$P<0.05$

TABLE II. *Relative increase of IOP and ICP with Pa_{CO_2}*

	Pa_{CO_2} (kPa)		
	2.66–5.05	5.05–7.71	7.71–10.24
$\Delta IOP/\Delta Pa_{CO_2}$			
Mean	0.016	0.017	0.02
SD	0.008	0.008	0.016
$\Delta ICP/\Delta Pa_{CO_2}$			
Mean	0.036	0.035	0.003
SD	0.016	0.039	0.027

slight delay, IOP (fig. 3) and ICP (fig. 4) decreased in a similar manner attaining a new steady state in about 10 min. Both pressures showed a significant linear correlation with Pa_{CO_2} ($P<0.001$). The percent decrease of each pressure during the first 5 min was plotted semilogarithmically to calculate half-times for the equilibration of Pa_{CO_2}, IOP and ICP (fig. 5). The following half-times were estimated from this: Pa_{CO_2} 82 s; IOP 70 s; ICP 75 s.

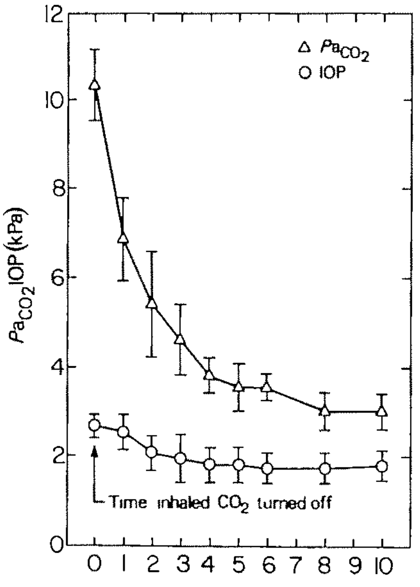

FIG. 3. Pa_{CO_2} and IOP during rapid washout of carbon dioxide in seven experiments.

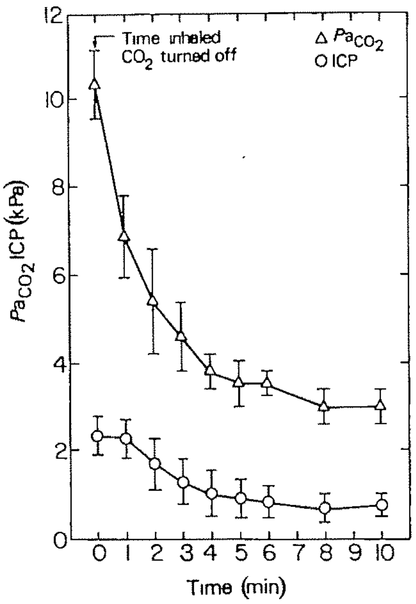

FIG. 4. Pa_{CO_2} and ICP during rapid washout of carbon dioxide in seven experiments.

DISCUSSION

Our data confirm previous findings that IOP increases with Pa_{CO_2} (Duncalf and Weitzner, 1963; Adams and Barnett, 1966; Meyer and Opitz, 1970; Samuel and Beuagie, 1974; Kaufmann, 1975) and suggest a linear relationship between the two pressures. IOP changes were not caused by cardiovascular factors when Pa_{CO_2} was allowed to stabilize, since HR and c.v.p. remained stable and m.a.p. decreased slightly at high arterial carbon dioxide tensions. During carbon dioxide washout, a transient decrease in m.a.p. might have influenced IOP and ICP and so reduced their half-times compared with that of Pa_{CO_2}.

The two most likely mechanisms by which carbon dioxide affects IOP are alteration of intraocular blood volume and altered formation of aqueous humour. The response of the choroidal and cerebral circulations to changes in Pa_{CO_2} in the baboon has been reported by Wilson, Strang and McKenzie, 1977. They found blood flow in both circulations varied directly with Pa_{CO_2}, the magnitude of the responses being very similar.

Spalter, Ten Eick and Nahas (1964) observed that hypercarbia caused intraocular vasodilatation

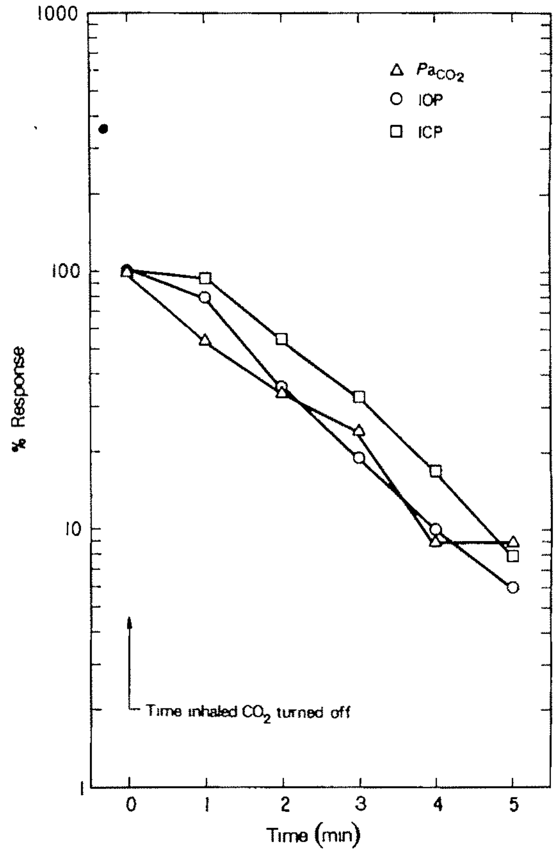

FIG. 5. Per cent total response during rapid washout of carbon dioxide (means of seven experiments).

while Alm and Bill (1972) found ocular blood flow to increase by 200–300% with increase in Pa_{CO_2}. The increase in IOP with hypercarbia is likely to result from an increase in intraocular blood volume. Compared with IOP, the response of ICP to changes in Pa_{CO_2} showed much greater variability, especially at the maximum Pa_{CO_2} studied. Since the autoregulation of the cerebral circulation seems to shift to a higher level with increase of Pa_{CO_2} (Haggendal, Nilsson and Norback, 1969), the small decrease in m.a.p. might have decreased perfusion. It also seems that increasing Pa_{CO_2} may produce a variable response in the cerebral circulation (Haggendal, Nilsson and Norback 1969). Compensatory mechanisms might also have interfered.

During sudden hyperventilation, Pa_{CO_2} decreases exponentially (Nunn, 1975). The half-time we found in monkeys was shorter than the 3–4 min described for man (Nunn, 1975).

IOP remained within a normal range in most of our experiments even at the maximum Pa_{CO_2} achieved. Moderate changes of Pa_{CO_2} appear to have little clinical significance, but hyperventilation should be considered and hypoventilation avoided when a low IOP is required. The rapid changes in IOP follow closely the changes in ICP and can be explained by alteration in intraocular blood volume.

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PRESSIONS INTRAOCULAIRE ET INTRACRANIENNE AU COURS D'UNE ALCALOSE ET D'UNE ACIDOSE RESPIRATOIRES

RESUME

Nous avons mesuré les pressions intraoculaire et intracranienne (IOP et ICP) à quatre différentes tensions du gaz carbonique artériel et par des techniques continues directes sur des singes Rhésus au cours d'une anesthésie effectuée à l'aide d'halothane et de protoxyde d'azote. L'accroissement de l'IOP a donné une corrélation significative avec la $Pa\text{CO}_2$ sur une plage de 2,66 à 10,24 kPa ($P < 0{,}001$). L'accroissement de l'ICP a donné une corrélation significative ($P < 0{,}001$) avec la Pa_{CO_2} sur une plage de 2,66 à 7,71 kPa, mais est restée stationnaire après. Lorsque la Pa_{CO_2} a décru rapidement, la Pa_{CO_2}, l'IOP et l'ICP ont décru d'une manière exponentielle, avec, des demi-temps similaires. Les changements rapides dans l'IOP et l'ICP peuvent probablement s'expliquer par une modification des volumes sanguins intraoculairs et intracraniens. Dans l'ensemble, l'IOP est restée dans une plage normale même au maximum de la Pa_{CO_2}.

INTRAOKULÄRER UND INTRAKRANIELLER DRUCK WÄHREND ATMUNGSALKALOSE UND AZIDOSE

ZUSAMMENFASSUNG

Die intraokulären und intrakraniellen Drucke bei Rhesusaffen wurden während der Anästhesie mit Halothan und Stickoxydul bei vier verschiedenen Arterienkohlendioxyddrücken im direkten kontinuierlichen Verfahren gemessen. Es zeigte sich eine bedeutende Wechselbeziehung zwischen Steigerungen des intraokulären Druckes und Pa_{CO_2} im Bereich von 2,66 bis 10,24 kPa ($P < 0{,}001$). Es zeigte sich auch eine bedeutende Wechselbeziehung zwischen Steigerungen des intrakraniellen Drucks und Pa_{CO_2} im Bereich von 2,66 bis 7,71 kPa ($P < 0{,}001$), aber danach stellte sich eine Abflachung ein. Als die Pa_{CO_2}, schell reduziert wurde, nahmen Pa_{CO_2}, intraokulärer und intrakranieller Druck exponentiell ab, und zwar mit ähnlichen Halbwerten. Die schnellen Änderungen des intraokulären und intrakraniellen Druckes lässt sich wahrscheinlich durch eine Änderung des intraokulären und intrakraniellen Blutvolumens erklären. Der intraokuläre Druck blieb auch bei maximaler Pa_{CO_2} innerhalb des normalen Bereiches.

PRESION INTRAOCULAR E INTRACRANEAL DURANTE LA ALCALOSIS Y ACIDOSIS

SUMARIO

Durante la anestesia con halotano y con óxido nitroso de monos Rhesus, se midieron las presiones intraocular e intracraneal (PIO y PIC), a cuatro diferentes tensiones arteriales de dióxido de carbono siguiendo técnicas continuas y directas. Los incrementos en la PIO se correlacionaron significativamente ($P < 0{,}001$) con la Pa_{CO_2}, oscilando entre 2,66 y 10,24 kPa. Los incrementos en la PIC correlacionaron significativamente ($P < 0{,}001$) con la Pa_{CO_2} entre 2,66 y 7,71 kPa, siguiendo un valor horizontal posteriormente. Cuando la Pa_{CO_2} se disminuyó rápidamente, la Pa_{CO_2}, la PIO y la PIC disminuyeron exponencialmente con tiempos medios similares. Los rápidos cambios en la PIO y en la PIC pueden explicarse, probablemente, por la variación de los volúmenes sanguíneos intracraneal e intraocular. La PIO permaneció, por regla general, dentro de la gama normal, incluso para el valor máximo de la Pa_{CO_2}.

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PHYSICOCHEMICAL CHANGES DURING HAEMORRHAGE AND FOLLOWING INFUSION

K. AONO, T. TANAKA, H. URAKAMI AND K. HARANO

SUMMARY

Interstitial fluid pressure (IFP) and plasma colloid osmotic pressure (plasma COP) were measured in dogs following acute haemorrhage and following the infusion of saline, 10% dextran 40 in saline and 3% dextran 40 in lactated Ringer's solution. Exsanguination decreased IFP, plasma COP and total plasma protein and albumin concentrations, and increased plasma glucose concentration and osmotic pressure. A massive infusion of physiological saline increased IFP, and decreased plasma COP and total plasma protein and albumin concentrations. The volume of saline infused correlated with the increase in IFP. When a 10% dextran 40 saline solution was used, there was a marked increase in plasma COP but a decrease in IFP. When 3% dextran 40 in lactated Ringer's solution was infused, IFP was little affected in the early stage, but gradually increased thereafter. Plasma COP increased slightly immediately after infusion, but remained near the pre-exsanguination value for at least 3 h.

During haemorrhagic shock there is a decrease in extracellular (interstitial) fluid along with the marked decrease in circulating blood volume. Although a relatively massive infusion of crystalloid solution can compensate for the deficiency of interstitial fluid, blood transfusion or an infusion of colloids is required, in addition, to maintain plasma colloid osmotic pressure (plasma COP). During such manipulations it is obvious that there will be shifts of fluid through peripheral vessels and that the conditions in the interstitial space will be affected.

In this study, interstitial fluid pressure (IFP) was measured continuously to assess conditions in the interstitial space (Guyton, 1963). The relationship between the changes in IFP and blood constituents (including plasma COP) were investigated to determine the fluid shifts through peripheral vessels during haemorrhagic shock and following infusion.

METHODS

Small perforated capsules (2.6 × 2.6 × 3.0 cm, modified from Guyton's method (1963)) were implanted subcutaneously, using full aseptic techniques, in the backs of six mongrel dogs, to determine IFP. Antibiotics were administered for 5 days to prevent infection. The capsules were punctured a few days before the definitive experiments were undertaken and, if the fluid they contained was clear, the absence of infection was assumed. The experiments were performed 4–6 weeks after the implantation of the capsules.

Anaesthesia was induced with thiamylal 75–125 mg i.v. and maintained with an air–halothane mixture (0.5–1.5%). The trachea was intubated and mechanical ventilation instituted. Teflon catheters were inserted into the femoral artery and vein for the continuous measurement of arterial and central venous pressures (c.v.p.). Teflon needles were carefully inserted into the implanted capsules and connected through an ultralow pressure transducer (Statham P-23-BB) to an amplifier (Burr–Brown Instrumentation amplifier). IFP was continuously recorded (Yokogawa Electric Technicorder F, Type 3052).

Once a stable IFP had been achieved (at least 30 min later), the dogs were exsanguinated such that the mean arterial pressure (m.a.p.) was decreased to about 30 mmHg within 10 min (mean blood volume removed was $31.1 \pm 8.9 \text{ ml kg}^{-1}$ (table I)). Exsanguination was stopped and the animals left for 30 min.

Group 1 (three dogs) (fig. 1). Physiological saline in a volume four times that of the blood removed was infused, followed 2 h later by an infusion over 30 min of a volume of 10% dextran 40 in saline solution equal to that of the blood loss.

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TABLE I. *Changes in interstitial fluid pressure, plasma colloid osmotic pressure, plasma total protein and albumin after exsanguination. There was a positive significant correlation between plasma COP and plasma albumin* $^{*}r = 0.860$ $(0.05 < P < 0.1)$; $^{**}r = 0.990$ $(P < 0.05)$

Dog No.	Body weight (kg)	Exsang. vol. (ml kg^{-1})	Interstitial fluid pressure (cm H_2O)			Plasma colloid osmotic pressure (cm H_2O)		
			Before	After	Diff.	Before	After	Diff.**
1	8.6	19.8	−2.39	−3.40	−1.01	16.4	15.6	−0.8
2	10.0	39.4	−12.50	−13.00	−0.50	22.0	16.0	−6.0
3	7.0	34.3	−1.55	−3.70	−2.15	22.8	20.0	−2.8
4	12.5	40.0	−2.37	−6.50	−4.13	30.1	26.3	−3.8
5	11.5	32.2	−0.81	−1.90	−1.09	24.0	20.0	−4.0
6	7.4	20.8	−2.60	−3.40	−0.80	24.2	17.8	−6.4
Mean	9.5	31.1	−3.70	−5.32	−1.61	23.3	19.3	−4.0
SD	2.2	8.9	4.36	4.05	1.35	4.4	3.9	2.1

Dog No.	Body weight (kg)	Exsang. vol. (ml kg^{-1})	Plasma total protein (g dl^{-1})			Plasma albumin (g dl^{-1})		
			Before	After	Diff.*	Before	After	Diff.**
1	8.6	19.8	—	—	—	—	—	—
2	10.0	39.4	6.1	5.0	−1.1	2.5	2.0	−0.5
3	7.0	34.3	5.8	5.3	−0.5	2.6	2.4	−0.2
4	12.5	40.0	6.8	6.2	−0.6	2.9	2.6	−0.3
5	11.5	32.2	5.7	5.3	−0.4	2.6	2.3	−0.3
6	7.4	20.8	5.6	4.7	−0.9	2.6	2.0	−0.6
Mean	9.5	31.1	6.0	5.3	−0.7	2.6	2.3	−0.4
SD	2.2	8.9	0.5	0.6	0.3	0.2	0.3	0.2

Group 2 (*three dogs*) (fig. 1). A volume of 3% dextran 40 in lactated Ringer's solution equal to that of the blood loss was infused over 30 min.

Blood samples were drawn from the catheters in the femoral veins into heparinized syringes and the blood was replaced with equal volumes of physiological saline solution.

Small quantities of blood were aspirated into glass capillaries and centrifuged at 11 000 rev min^{-1} for 5 min and the haematocrit determined. The ice water-cooled residual blood samples were immediately centrifuged at 4 °C to obtain plasma. Plasma COP was measured with a recorder-equipped Knauer membrane osmometer

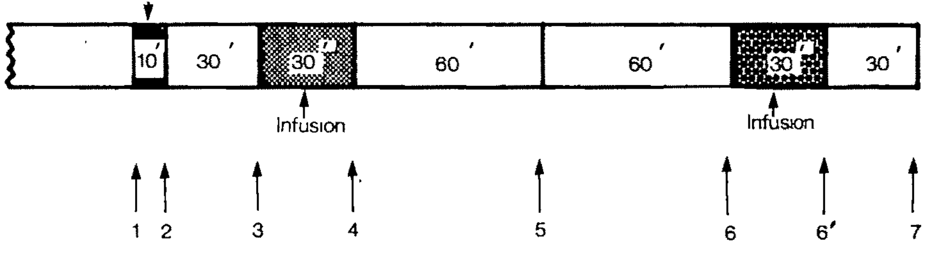

FIG. 1. Experimental procedures. After a steady state was obtained, the dogs were exsanguinated such that m.a.p. decreased to about 30 mm Hg in 10 min. Infusion was started at 30 min after exsanguination. First infusion: group 1 = normal saline (blood loss × 4); group 2 = 3% dextran 40 in lactated Ringer's solution (blood loss × 1). Second infusion: 10% dextran 40 in saline (blood loss × 1) only in group 1. Sample 6' indicates blood sampling only in group 1.

utilizing replacement physiological saline after a mean had been reached through four or five substitutions of the sample. Plasma osmotic pressure was measured three times, using a Knauer Halb-mikro-osmometer, and the average value calculated. Total plasma protein concentration was determined by the biuret reaction test, a white turbidity indicating the presence of dextran. Plasma albumin and glucose concentrations were determined by the bromcresol green method and enzyme method with hexokinase and NADPH (Böhringer's glucose HK test), respectively.

RESULTS

Changes following exsanguination

In all animals there was a decrease in IFP and plasma COP, the mean decreases being 1.61 and 4.0 cm H_2O, respectively (table I). However, there was no significant correlation between the decreases in IFP and plasma COP and there were no correlations between these indices and blood loss. There was a sharp decrease in IFP immediately after exsanguination, following which a stable value was attained (figs 2, 5). Total plasma protein and albumin concentrations decreased in all animals (table I). There was a positive significant correlation between the decreases in plasma COP and plasma albumin concentration ($r = 0.990$, $P < 0.05$), but not between plasma COP and total plasma protein concentration ($r = 0.860$, $0.05 \leq P \leq 0.1$) (table I).

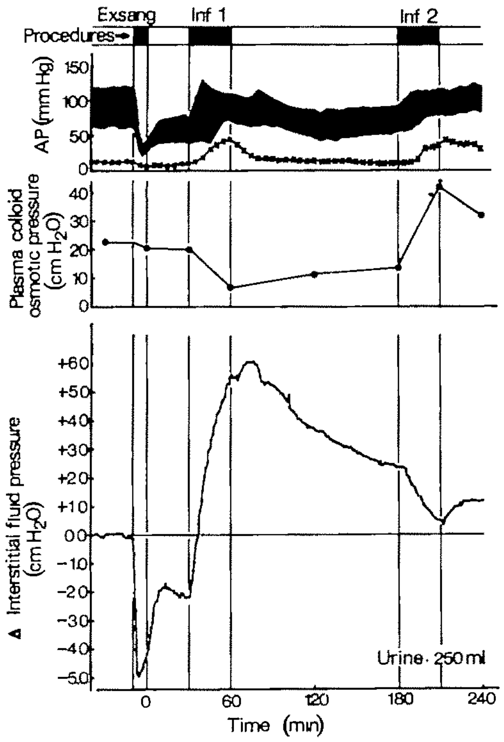

FIG. 2. Typical course of findings in the exsanguinated and treated dog (No. 3). Exsang = exsanguination (34.3 ml kg^{-1}); Inf 1 = Saline infusion; Inf 2 = infusion of 10% dextran in saline.

The plasma osmotic pressure and glucose concentration were determined in four animals immediately after and 30 min after exsanguination. Increases in these values were seen in all except one animal (immediately after exsanguination in dog no. 4 (table II)). There was no significant correlation between these increases in the two variables.

Effects of fluid infusion

The rapid infusion of physiological saline resulted in a decrease in plasma COP to half the control value (value before exsanguination) (fig. 2). IFP (values plotted as differences from mean control values), which decreased by about 2 cm H_2O after exsanguination, increased suddenly by 8 cm H_2O. Arterial pressure and CVP increased transiently during infusion, and IFP gradually decreased after infusion, but did not reach the previous control values. Arterial pressure did not return to the value before exsanguination following a massive infusion of normal saline. When a 10% dextran 40 in saline solution was given 2 h after the infusion of physiological saline, COP increased markedly from 13.4 to 42.0 cm H_2O and IFP returned almost to its control value. (Mean plasma COP in five samples taken after use of 10% dextran 40 in saline solution was 124.8 cm H_2O.) In group 1, plasma COP and plasma protein concentrations decreased during exsanguination and the infusion of saline before increasing slowly thereafter (fig. 3). A significant correlation was observed between the volume of saline infused and the rate of increase of IFP (ΔIFP) ($r = 0.816$, $P < 0.05$) (fig. 4).

In group 2 (fig. 5) IFP decreased slightly in the early stage of the infusion of 3% dextran 40 in lactated Ringer's solution and then progressively increased thereafter. (Mean plasma COP in five samples taken after use of 3% dextran 40 in lactated Ringer's solution was 38.0 cm H_2O.) Arterial pressure increased to greater than the control value for 3 h after infusion while c.v.p., which increased during infusion, gradually decreased to its control value within 3 h after the infusion.

TABLE II. *Changes in plasma glucose concentration and osmotic pressure after exsanguination*

Dog No.	Time after exsang. (min)	Plasma glucose (mg dl^{-1})			Plasma osmotic pressure (mosmol litre^{-1})		
		Before	After	Diff.	Before	After	Diff.
3	0	102	199	97	292	295	3
	30	102	193	91	292	296	4
4	0	105	101	−4	298	298	0
	30	105	111	6	298	301	3
5	0	86	118	32	291	296	5
	30	86	126	40	291	306	15
6	0	127	326	199	303	316	13
	30	127	282	155	303	310	7
Mean	0	105±17	186±103	81±89	296±6	301±10	5.3±5.6
±SD	30	105±17	178±78	73±65	296±6	303±6	7.3±5.4

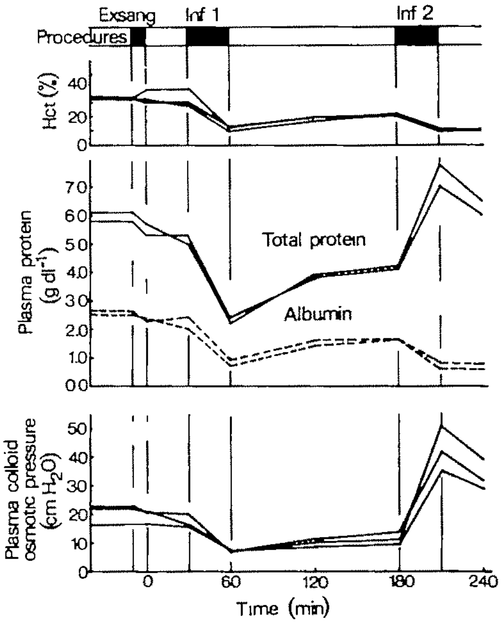

FIG. 3. Changes in haematological findings in exsanguinated and treated dogs. Abbreviations as figure 2.

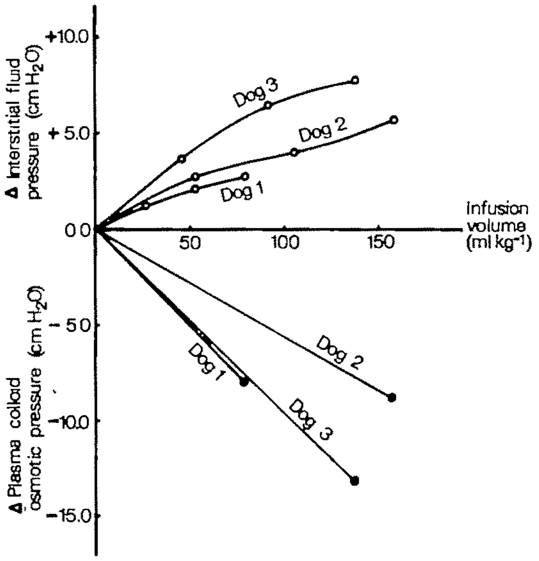

FIG. 4. Relationship between infused saline volume and interstitial fluid pressure (○) or plasma colloid osmotic pressure (●) during infusion after exsanguination.

The infusion of 3% dextran 40 in lactated Ringer's solution increased plasma COP initially, after which it remained near the control value for at least 3 h (figs 5, 6). Plasma albumin concentration decreased markedly immediately after the infusion (fig. 6). There was no correlation between the volume of fluid infused and plasma COP, but there was a tendency after infusion whereby the greater the plasma COP, the lower the IFP (fig. 7).

DISCUSSION

Exsanguination of mongrel dogs induced decreases in IFP and plasma COP in all animals. IFP is considered to be less than atmospheric pressure in the normal state (Guyton, 1963, 1965; Guyton, Granger and Tayler, 1971) and to increase when interstitial fluid accumulates. As long as IFP is less than atmospheric it is considered to correlate with the increase in interstitial fluid volume. On the basis of these findings, changes in hydration in the

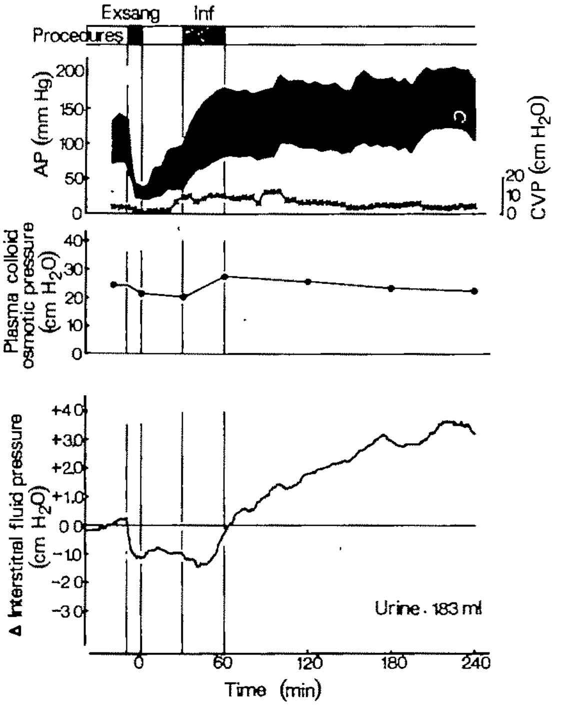

FIG. 5. Typical course of findings in the exsanguinated and treated dog (No. 5). Exsang = exsanguination (32.2 ml kg^{-1}); Inf = infusion of 3% dextran 40 in lactated Ringer's solution.

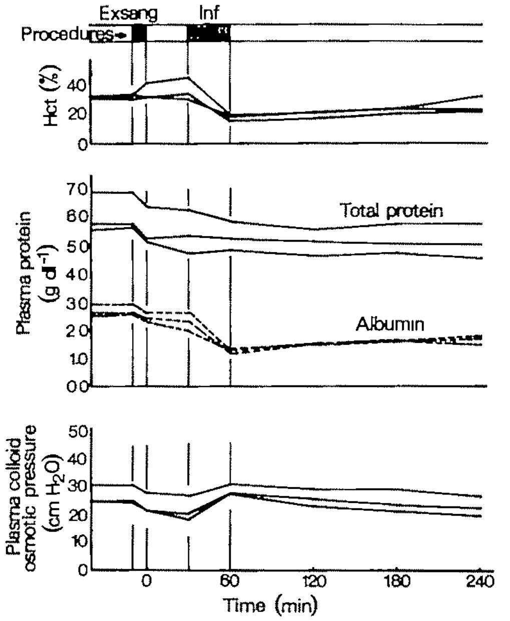

FIG. 6. Changes in haematological findings in exsanguinated and treated dogs. Abbreviations as figure 5.

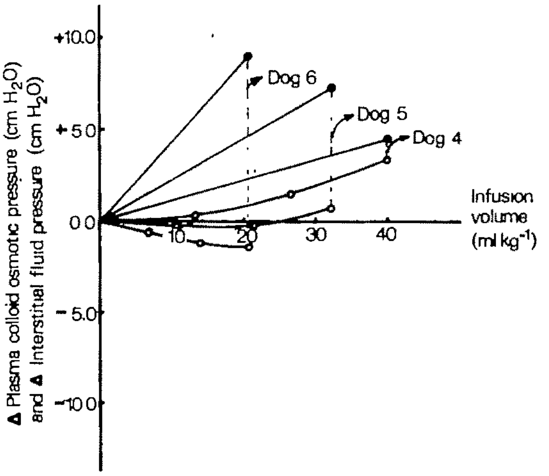

FIG. 7. Relationship between infused volume of 3% dextran 40 in lactated Ringer's solution and interstitial fluid pressure (○) or plasma colloid osmotic pressure (●) during infusion after exsanguination.

interstitial space may be estimated continuously through continuous recording of IFP. Continuous monitoring of interstitial fluid volume using radioisotopes is not feasible. Hopkinson and colleagues (1968) and Wolcott, Malinin and Wu (1976) observed that IFP decreased during haemorrhagic shock in dogs and rabbits, and the former also found IFP to recover after infusion of lactated Ringer's solution.

Two explanations are possible to account for the decreases in IFP and plasma COP during exsanguination. First, a shift of interstitial fluid, which has a lower protein concentration and COP than plasma, into intravascular compartments to compensate for the loss in circulating blood volume and, second, a shift of lymph to the venous circulation system.

However, the second explanation lacks conviction as it has been reported that only a transient increase (to 3–4 ml min^{-1}) was observed in thoracic duct lymph flow when approximately 30% of circulating blood volume was lost in animal experiments (Cope and Litwin, 1962), and that thoracic duct lymph flow was unchanged when 15% of the circulating blood was removed (Zollinger, 1972).

Total plasma protein and albumin concentrations decreased as a result of exsanguination. However, decreases in plasma COP correlate only with decreases in plasma albumin concentration, and since albumin has a smaller molecular weight than globulin, it suggests that plasma albumin is a major factor contributing to COP.

In our study, plasma osmotic pressure and blood sugar concentration increased. Järhult and colleagues (1972) reported that, in cats, rapid blood loss induced an increase in arterial blood sugar concentration and plasma osmotic pressure, followed by similar increases in venous blood. Based on these data, the increase in plasma osmotic pressure was thought to be the result of the increase in blood sugar (Järhult, 1973). They reported that the greater the blood loss, the greater the increase in blood sugar concentration, and that this indicated that an increase in osmotic pressure was a mechanism which compensated for blood loss (Järhult et al., 1976).

Therefore, the low IFP during exsanguination is believed to be in part a result of the shift of interstitial fluid into the intravascular space, a shift induced by the decrease in the net driving power which normally forces plasma components into the tissue. The slight but consistent decrease in COP as a result of haemorrhage also supports such a shift of fluid because interstitial fluid has a lower COP than plasma.

In our study, the group 1 dogs were infused with a volume of saline solution equal to four times that of the blood loss. The ratio of plasma to interstitial fluid volume being regarded as 1 : 3, a four-fold volume is required to compensate for blood loss as the saline spreads evenly through both interstitial and intravascular spaces. The massive infusion of saline brought about a linear increase in IFP and decreased the haematocrit (Hct), plasma COP and total plasma protein and albumin concentrations. This implied haemodilution was followed by a rapid fluid shift into the interstitial space. During the 2 h following the infusion of saline, Hct, plasma COP and protein concentrations tended to increase gradually while IFP decreased. CVP and arterial pressure decreased. These facts indicate that water may have been excreted as urine.

The infusion of 10% dextran 40 in saline solution markedly increased plasma COP, arterial pressure and CVP while IFP decreased, indicating a shift of interstitial fluid into the intravascular space. The false increase in total plasma protein concentration after infusion of 10% dextran 40 (figs 2, 3) is believed to be a result of the turbid chemical reaction between biuret reagent and dextran.

In group 2, the infusion of 3% dextran 40 in lactated Ringer's solution increased plasma COP slightly while Hct and plasma albumin concentration decreased. IFP increased slightly or remained unchanged in the early stage of the infusion but increased progressively thereafter. These results indicate that there may be a slight shift of interstitial fluid into the intravascular space, mainly as a result of the increase in plasma COP, particularly in the early stage, and that dextran 40 may subsequently move slowly into the interstitial space.

In conclusion, a rapid haemorrhage will induce a fluid shift from the interstitial to the intravascular space and result in a decrease in interstitial fluid. If saline is infused rapidly it quickly passes through the peripheral vascular wall, whereas a reverse shift of fluid takes place when 10% dextran 40 in saline solution is infused. When 3% dextran 40 in lactated Ringer's solution is infused, it remains in the vessels during the early stage of infusion and then enters the interstitial space. The massive infusion of dextran 40 in saline solution may result in hazardous conditions later on.

ACKNOWLEDGEMENTS

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CHANGEMENTS PHYSICO-CHIMIQUES PENDANT UNE HEMORRAGIE ET APRES UNE PERFUSION

RESUME

On a mesuré sur des chiens la pression du liquide interstitiel (IFP) et la pression osmotique colloïdale du plasma (plasma COP) après une hémorragie aiguë et après la perfusion d'une solution saline, de 10% de dextrane 40 dans une solution saline et de 3% de dextrane 40 dans une solution physiologique lactée de Ringer. L'exsanguination a fait baisser l'IFP et la plasma COP de même que les concentrations totales de protéines et d'albumine du plasma, tout en faisant augmenter les concentrations de glucose dans le plasma et la pression osmotique. Une perfusion massive de soluté physiologique a fait augmenter l'IFP et diminuer la plasma COP de même que les concentrations totales de protéines et d'albumine dans le plasma. Le volume de soluté physiologique perfusé a été en corrélation avec l'augmentation de l'IFP. Lorsqu'on a utilisé une solution saline comprenant 10% de dextrane 40, on a constaté une forte augmentation de la plasma COP, mais une diminution de l'IFP. Lorsqu'on a fait une perfusion d'une solution physiologique lactée de Ringer comprenant 3% de dextrane, l'IFP n'a été que très faiblement affectée au début, mais a graduellement augmenté par la suite. La plasma COP a légèrement augmenté immédiatement après la perfusion, mais elle est restée tout près des valeurs antérieures à l'exsanguination pendant au moins trois heures.

PHYSICOCHEMISCHE ÄNDERUNGEN WÄHREND BLUTUNG UND NACH INFUSION

ZUSAMMENFASSUNG

Der interstitielle Flüssigkeitsdruck und der osmotische Druck des Plasmakolloids wurden bei Hunden nach akuter Blutung und nach Infusion von einer physiologischen Kochsalzlösung, 10% Dextran 40 in physiologischer Kochsalzlösung und 3% Dextran 40 in Laktat-Ringer-Lösung gemessen. Entblutung führte zu einer Abnahme des interstitiellen Drucks, des osmotischen Drucks des Plasmakolloids, und der Gesamtkonzentrationen von Plasmaprotein und Albumin, und zu einer Zunahme der Plasmaglukosekonzentration und des osmotischen Drucks. Eine massive Infusion von physiologischer Kochsalzlösung führte zu einer Zunahme des interstitiellen Drucks und einer Abnahme des osmotischen Drucks des Plasmakolloids und der Gesamtkonzentration von Plasmaprotein und Albumin. Es bestand eine Wechselbeziehung zwischen dem Volumen der Kochsalzlösung und der Zunahme des interstitiellen Drucks. Als eine 10% Dextran 40 Kochsalzlösung verwendet wurde, stellte sich eine auffallende Zunahme des osmotischen Drucks des Plasmakolloids ein, aber auch eine Abnahme des interstitiellen Drucks. Als 3% Dextran 40 in einer Laktat-Ringer-Lösung eingeflösst wurde, hatte es zunächst keinen Einfluss auf den interstitiellen Druck, aber das änderte sich allmählich danach. Der osmotischer Druck des Plasmakolloids nahm gleich nach der Infusion etwas zu, blieb aber in der Nähe des Wertes vor der Entblutung mindestens drei Stunden lang stehen.

CAMBIOS FISICOQUIMICOS DURANTE LA HEMORRAGIA Y A RAIZ DE LA INFUSION

SUMARIO

Se midieron en perros la presión del flúido intersticial (PFI) y la presión osmótica coloidal del plasma (plasma POC), como consecuencia de una hemorragia aguda y a raíz de la infusión de una solución salina, 10% de dextrana 40 en la solución salina y 3% de dextrana 40 en la solución Ringer lactada. La pérdida de sangre produjo la disminución de la PFI, de la presión POC, así como las concentraciones totales de albúmina y de proteina en el plasma, e incrementó la concentración de glucosa en el plasma y la presión osmótica. Una infusión masiva de solución salina fisiológica incrementó la PFI y disminuyó la POC, así como las concentraciones totales de albúmina y de proteina en el plasma. El volumen de la solución salina adminstrada vino correlacionada con el incremento de la PFI. Cuando se usó una solución salina con dextrana 40 al 10%, tuvo lugar un marcado incremento de la POC pero también una disminución de la PFI. Se administrós una solución de Ringer lactada con dextrana 40 al 3%, la PFI no quedó muy afectada en un principio, incrementando gradualmente en las fases posteriores. La COP aumentó ligeramente justo después de la infusión, pero permaneció cerca del valor previo a la pérdida de sangre por espacio de por lo menos 3 horas.

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RHABDOMYOLYSIS, MYOGLOBINURIA AND HYPERPYREXIA CAUSED BY SUXAMETHONIUM IN A CHILD WITH INCREASED SERUM CREATINE KINASE CONCENTRATIONS

K. B. LEWANDOWSKI

SUMMARY

Rhabdomyolysis, myoglobinuria, hyperpyrexia, muscle weakness and stiffness occurred in a 4-yr-old boy after halothane anaesthesia and a single dose of suxamethonium. Neurological examination of the patient and his mother revealed no physical abnormality although in both the serum creatine kinase and lactic dehydrogenase concentrations were increased. McArdle's disease was excluded by a normal response to an ischaemic work test.

Apparently normal individuals may show minimal signs of muscle destruction following the administration of suxamethonium or halothane or both, as demonstrated by slight increases in serum concentrations of creatine phosphokinase (CK), but without clinical manifestation. Subjects with an increase in their resting serum CK concentration may develop significant destruction of striated muscles with clinical signs varying from muscle weakness, hyperaesthesia, myoglobinuria, mild increase in body temperature, mild metabolic acidosis, and marked increases in concentrations of their serum enzyme, to fulminating hyperpyrexia, grave hypoxia, marked disorder of serum electrolyte concentrations and death.

A case of anaesthesia complicated by rhabdomyolysis, myoglobinuria, muscle rigidity and a moderate increase in body temperature is presented.

CASE REPORT

A previously healthy, 4-yr-old boy presented for tonsillectomy. He had never been anaesthetized before, had no allergies and was considered a good anaesthesia risk. Before operation the arterial pressure, heart rate, body temperature, haemoglobin concentration and packed cell volume were normal. Forty-five minutes before induction anaesthesia, pethidine 20 mg and atropine 0.25 mg were given i.m. (body weight 19 kg). Anaesthesia was induced with nitrous oxide 4 litre $\min^{-1}$, oxygen 4 litre $\min^{-1}$ and 1.5% halothane given by mask. Breathing was spontaneous. Suxamethonium 25 mg was injected i.v.; muscle fasciculation was unusually strong and the jaw was not relaxed. Intubation of the trachea was performed with difficulty, although no additional neuromuscular blocker was given. There was no cyanosis. Anaesthesia was continued with a mixture of nitrous oxide and halothane in oxygen with spontaneous breathing. At the beginning of the operation the patient received thiopentone 25 mg because his limbs were stiff and the level of anaesthesia was considered inadequate. The later course of anaesthesia was judged to be normal except for slight stiffness of the upper limbs and a heart rate of 140–160 beat $\min^{-1}$ Breathing was satisfactory and there was no cyanosis. Body temperature was not monitored. The operation lasted 30 min. The trachea was extubated, oxygen administered via a face mask and the patient regained consciousness normally.

Five hours later dark brown urine was voided and rhabdomyolysis and myoglobinuria were suspected. The rectal temperature was 38 °C; measurements were now made at frequent intervals. Oxygen 6 litre $\min^{-1}$ was given via a mask. The rectal temperature never exceeded 38.2 °C. Body temperature was decreased to normal with electric fans. The possibility of malignant hyperpyrexia was appreciated and provision made for rapid lowering of the body temperature. The patient was conscious, orientated, and willing to drink water.

Examination of urine showed a positive test for occult blood, but the urine contained no red cells on microscopic examination. A test for urine ketones was positive. The urine contained no

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sugar and blood glucose concentration was normal. Electrophoretic examination of the urine showed large amounts of myoglobin (results available several days later).

There was a moderate, compensated metabolic acidosis and sodium bicarbonate infusion was not necessary.

The concentrations of the serum enzymes creatine phosphokinase (CK), aldolase, asparate aminotransferase lactate (ASAT), ALAT, and lactic dehydrogenase (LD) were markedly increased (table I). Serum potassium and sodium concentrations were normal.

Urine output was maintained by large amounts of oral fluids. During the first 12 h following surgery the patient voided spontaneously 300 ml of dark brown urine; diuretics or mannitol were not considered necessary, especially as the serum creatinine concentration remained normal. The urine was brown for 24 h, becoming clear later. Urinary output was satisfactory.

During the first 48 h following operation the patient was unable to stand or walk without help because of muscle weakness. Chest x-ray was normal. The clinical condition of the patient improved gradually and on the 3rd day after operation he was discharged fit and well. However, with the exception of serum CK concentration, which decreased once to a normal value, the concentrations of the serum enzyme remained increased. Neurological examination revealed no physical abnormalities and a histopathological examination of muscle, and the electromyograph, were normal.

One month later, and on three later occasions, serum creatine kinase concentration was still increased.

The boy's mother was also without symptoms of muscle disease, although she did have increased serum creatine phosphokinase and lactic dehydrogenase concentrations of 116 u. litre^{-1} and 750 u. litre^{-1} respectively. The mother had been anaesthetized previously, but the course of anaesthesia had been uneventful despite the use of myoglobinuria triggering agents. Her chest x-ray was normal.

Neither the patient nor his mother had any evidence of myotonic dystrophy and McArdle's disease was excluded by an ischaemic work test. It was not possible to examine the father of the patient.

TABLE I. *Results of clinical laboratory tests. Myoglobinuria present only on day of operation. CK = serum creatine kinase; ASAT = serum aspartate aminotransferase lactate; ALAT = serum alanine amnotransferase*

Normal Value	Day of op.	After operation 1st day	2nd day	1 month
CK 0–50 u. litre^{-1}	32000	—	26	180
Aldolase 0–3.1 u. litre^{-1}	41	—	—	1.6
LD 0–400 u. litre^{-1}	1360	—	2642	460
ASAT 0–40 u. litre^{-1}	580	1200	868	16
ALAT 0–40 u. litre^{-1}	163	260	362	11
pH (unit)	7.43	7.38	Normal	
$P\text{co}_2$ (kPa)	3.9	4.0	Normal	
Base excess (mmol litre^{-1})	−4.5	−4.8	Normal	
Serum creatinine 50–110 μmol litre^{-1}	86	90		

DISCUSSION

Myoglobinuria is a chemical finding which denotes prior muscle damage but is not a specific entity in itself. The factors which may cause the phenomenon of myoglobinuria are: congenital errors in metabolism (McArdle's disease because of absent muscle phosphorylase), muscle trauma (crush injury), and poisoning of the metabolic system (alcohol or barbiturate intoxication) (Auerbach et al., 1973).

Myoglobinuria may occur rarely after general anaesthesia. Suxamethonium, especially when given during halothane anaesthesia, causes an increase in the concentrations of the serum enzymes normally found in large amounts in muscle (Auerbach et al., 1973). Previous studies have shown that the administration of suxamethonium to normal individuals results in alterations in muscle membrane integrity expressed as an increase in the concentrations of creatine phosphokinase (CK) (Tammisto and Airaksinen, 1966). Halothane not only potentiates the effect of suxamethonium, but also produces the same changes when administered alone (Pearson, Beck and Bladh, 1957), although to a lesser extent.

In 1966 it was observed that the administration of suxamethonium to a number of children did not produce muscular relaxation, but caused paradoxical muscle spasm and rigidity of striated muscles which made endotracheal intubation difficult. This was followed by increase of body temperature to 41 °C, myoglobinuria on the first day after anaesthesia, and muscle weakness and hyperaesthesia for several days. Increased concentrations of creatine phosphokinase, aldolase, lactic dehydrogenase and other enzymes in the serum was also observed (Auerbach et al., 1973). Suxamethonium caused a type of muscle destruction known as rhabdomyolysis. Myoglobinuria following the use of suxamethonium was reported by McLaren (1968). Suxamethonium may cause more serious adverse reaction—malignant hyperpyrexia. An untoward reaction to suxamethonium is probably attributable to a genetic alteration of the receptor protein, resulting in changes ranging from muscle rigidity with minimal rhabdomyolysis and a slight increase in body temperature to massive myolysis, myoglobinaemia, myoglobinuria, malignant hyperpyrexia, cyanosis, metabolic acidosis and possibly death (Aldrete et al., 1971; Auerbach et al., 1973; Lewandowski, Hollmén and Reunanen, 1975).

In this patient rhabdomyolysis and myoglobinuria were suspected in the period soon after anaesthesia (dark urine, stiffness and weakness of muscles, and moderate increase of body temperature). The diagnosis was confirmed by the increased concentration of serum enzymes, metabolic acidosis, and a positive reaction to blood in urine, although with the absence of red cells on microscopic examination of the urine specymen. Urine was sent for electrophoretic examination, but the result for myoglobin (strongly positive) was not available for some days.

Unfortunately, the body temperature was not measured during anaesthesia, neither was any explanation sought for peroperative tachycardia and muscle stiffness.

Rhabdomyolysis and pyrexia may have occurred because, instead of causing the usual transitory muscle fasciculation followed by relaxation, suxamethonium produced fasciculations followed by massive and sustained muscle contraction.

Although the increase in serum CK concentration was significant in this patient, there were no serious disturbances in heart rhythm, in contrast to the report by Schaer and colleagues (1977) who observed that rhabdomyolysis (muscle destruction) twice caused cardiac arrest during anaesthesia because of rapid changes in serum electrolyte concentrations (hypocalcaemia).

In this patient the myoglobinuria was treated by giving large amounts of oral fluids, as he was conscious and willing to drink. Catheterization of the bladder was not necessary. However, suxamethonium-induced myoglobinuria may cause acute renal failure and the urine output should be measured. If necessary, normal diuresis should be maintained with appropriate i.v. fluids, therapy and diuretics (frusemide) or mannitol (Benlike and Jarnum, 1964); serum creatinine and potassium concentrations must be measured and corrected if necessary, as must any metabolic acidosis.

Previous studies (Airaksinen and Tammisto, 1966) have shown that myoglobinuria has occurred after four intermittent doses of suxamethonium given during halothane anaesthesia and that precurarization protected the patient from an increase in serum creatine phosphokinase and prevented myoglobinuria (Tammisto, Leikkonen and Airaksinen, 1967). Moore, Watson and Summary (1976) showed that two doses of suxamethonium caused myoglobinuria. In the present study rhabdomyolysis and myoglobinuria occurred after a single dose of suxamethonium.

Incomplete muscular relaxation, rigidity or stiffness of striated muscles or unexplained tachycardia during anaesthesia must be considered as warning signs of myoglobinuria or malignant hyperpyrexia (MH). The body temperature must be measured, and in the event of MH appropriate treatment instituted (Relton, Britt and Steward, 1973). Another important, but late, sign of rhabdomyolysis in previously healthy subjects is the appearance early in the postoperative period of muscle weakness (inability to sit or walk) in patients in whom residual neuromuscular blockade, recurarization, abnormalities in serum electrolyte concentrations (hyponatremia, hypokalaemia, periodical familial hypokalaemia) can be excluded.

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RHABDOMYOLYSE, MYOGLOBINURIE ET HYPERPYREXIE CAUSEES PAR LE SUXAMETHONIUM CHEZ UN ENFANT AYANT UNE FORTE CREATINE KINASE DU SERUM

RESUME

Il s'est produit une rhabdomyolyse, une myoglobinurie, de l'hyperpyrexie et une faiblesse, de même qu'un raidissement des muscles chez un enfant de quatre ans, après qu'il ait été anesthésié à l'halothane et à l'aide d'une seule dose de suxaméthonium. L'examen neurologique du patient et de sa mère n'a révélé aucune anomalie physique bien que sur ces deux personnes les concentrations de créatine kinase et de déshydrogenase lactique dans le sérum aient été élevées. La maladie de McArdle a pu être exclue du fait d'une réaction normale à un test de travail ischémique.

RHABDOMYOLYSE, MYOGLOBINURIE UND HYPERPYREXIE INFOLGE VON SUXAMETHONIUM-VERABREICHUNG BEI EINEM KIND MIT GESTEIGERTER SERUMKREATINKINASE

ZUSAMMERFASSUNG

Rhabdomyolyse, Myoglobinurie, Hyperpyrexie, Muskelschwäche und Steifheit setzten bei einem 4-jährigen Jungen nach Halothananästhesie und einer einzelnen Dosis von Suxamethonium ein. Eine neurologische Untersuchung des Patienten und seiner Mutter zeigte keine physische Abnormalität, obwohl die Serumkreatinkinase -und Dehydrogenasekonzentrationen bei beiden gesteigert waren. McArdle'sche Krankheit wurde durch eine normale Reaktion auf eine ischämische Funktionsprüfung ausgeschaltet.

RHABDOMIOLISIS, MIOGLOBINARIA E HIPERPIREXIA OCASIONADAS POR EL SUXAMETONIO EN UN NIÑO QUE PRESENTABA UN INCREMENTO DE QUINASA CREATINA EN EL SUERO

SUMARIO

Rhabdomiolisis, mioglobinaria, hiperpirexia, debilidad muscular y rigidez se presentaron en un niño de 4 años después de la anestesia con halotano y una única dosis de suxametonio. El examen neurológico del paciente y de su madre no reveló anormalidades físicas, aunque en ambos habían aumentado las concentraciones de las deshidrogenasas lácticas y de la quinasa creatina de suero. La enfermedad de McArdle se descartó a raíz de obtener una respuesta normal a una prueba isquémica.

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USE OF SODIUM NITROPRUSSIDE FOR DELIBERATE HYPOTENSION DURING PREGNANCY

D. RIGG AND A. MCDONOGH

SUMMARY

Deliberate hypotension with sodium nitroprusside was used to facilitate surgery for cerebral aneurysm in two pregnant patients, with no apparent adverse effects on the fetus. The evidence that nitroprusside is harmful to the fetus appears to arise from one animal experiment in which insufficient detail of dosage was given.

Subarachnoid haemorrhage from ruptured intracranial aneurysm is uncommon during pregnancy, the frequency being less than 1 per 10 000 pregnancies. Surgical intervention creates risks for the mother and her unborn child, but has been shown to be the best form of management (Robinson, Hall and Sedzimir, 1972). The method of anaesthesia is not so clear, although most units now favour deliberate hypotension during direct surgery to the aneurysm (Donchin et al., 1978; Minielly, Yuzpe and Drake, 1979). For the non-pregnant patient sodium nitroprusside has marked advantages over other methods and has been used widely in recent years. Some doubt has been cast on the use of nitroprusside in the pregnant patient because of risk to the fetus from high cyanide concentrations in fetal blood (Lewis et al., 1977). Sodium nitroprusside has been used for aneurysm surgery in two pregnant patients at our hospital in recent years.

CASE REPORTS

Patient 1

A 31-year-old lady in her second pregnancy, weighing 57 kg, suffered a subarachnoid haemorrhage at 20 weeks of pregnancy. Angiography demonstrated an elongated aneurysm at the upper end of the basilar artery. Her past history included pre-eclamptic toxaemia during the last pregnancy and subsequent persistent hypertension which had been difficult to control. Her treatment at the time of admission was propranolol 40 mg and alpha-methyldopa 250 mg both thrice daily. Arterial pressure was 140/100 mm Hg. The patient had neck stiffness and photophobia. Surgical intervention was planned to follow a short period of bed rest and sedation.

Anaesthesia comprised thiopentone, myoneural blockade, nitrous oxide and a short acting narcotic. Arterial pressure was monitored via an indwelling radial artery catheter. The pressure proved difficult to control and a combination of hypotensive agents consisting of halothane, propranolol, sodium nitroprusside, hydrallazine and pentolinium tartrate was required during the procedure to allow surgical control to be achieved. The course after operation was complicated by severe hypertension which required a nitroprusside infusion for 48 h while the propranolol and alpha-methyldopa treatment was restabilized. The total dose of sodium nitroprusside was 40 mg during and approximately 50 mg in the 48 h after operation. The patient developed acute hydrocephalus which required a ventriculo-peritoneal shunt.

Nineteen weeks after operation, the patient was delivered of a girl weighing 3570 g and having Apgar scores of 5, 6 and 10 at 1, 5 and 10 min respectively. The baby appeared normal at birth and has since progressed satisfactorily.

Patient 2

A 26-year-old lady, also in her second pregnancy, weighing 45 kg was admitted with a 2-day history of severe fronto-occipital headache. She was 20 weeks pregnant. There was no relevant past medical history. Physical examination revealed a slightly disorientated patient with marked neck stiffness. Arterial pressure was normal. Lumbar

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puncture confirmed the diagnosis of subarachnoid haemorrhage. Angiography demonstrated an aneurysm at the junction of the vertebral and basilar arteries. She underwent surgery after a period of bed rest and sedation. The method of anaesthesia was the same as in patient 1. Arterial pressure was monitored continuously by an indwelling radial artery catheter. Deliberate hypotension was achieved by a combination of halothane and sodium nitroprusside. The pressure was maintained at a systolic pressure of 70 mm Hg during aneurysm dissection and clip application, but brisk bleeding at this stage necessitated that the pressure be reduced rapidly by an increase in the rate of sodium nitroprusside infusion until bleeding was controlled surgically. The total dose of sodium nitroprusside was 60 mg.

The course after operation was uneventful except for a partial right 6, 10 and 12 cranial nerve deficit. Pregnancy progressed to term when a live 3205-g female was delivered by application of low forceps under extradural anaesthesia. Apgar scores at 1 and 5 min were 9–10. Subsequent progress has been normal.

DISCUSSION

In cases of ruptured cerebral aneurysm during pregnancy surgery is now accepted as the treatment most likely to lead to survival of mother and child. Robinson, Hall and Sedzimir (1972), in a series of 14 patients found a mortality of five out of eight patients treated non-surgically and a high frequency of abortion and still birth while, in six women treated surgically, all mothers and babies were alive and well at the time of the study. However, Robinson, Hall and Sedzimir (1972) believed that hypothermia should be used and that the use of hypotension and osmotic diuretics was dangerous. More recently, Minielly, Yuzpe and Drake (1979) and Donchin and others (1978) have successfully used deliberate hypotension during aneurysm surgery in pregnancy.

Sodium nitroprusside has been used in recent years to achieve deliberate hypotension during cerebral aneurysm surgery. It is reliable, evanescent and does not lead to any postoperative postural hypotension. However, several recent articles (Ring et al., 1977; Donchin et al., 1978; Snyder, Wheeler and James, 1979; Wheeler et al., 1980) have warned of the potential danger to the fetus of using sodium nitroprusside during pregnancy. All of these articles refer to work reported in 1977 by Lewis and others, in which eight near-term normotensive ewe preparations were studied. Maternal arterial pressure was decreased by a nitroprusside infusion. Fetal cyanide concentrations were not significantly increased in four animals which required only a low rate of nitroprusside infusion. The other four animals required a steadily increasing dose of nitroprusside and showed a marked accumulation of maternal and fetal cyanide with fetal concentrations significantly greater than maternal values. These four fetuses expired *in utero*.

Nitroprusside toxicity in animals resistant to its hypotensive effects has been well demonstrated previously by McDowall and others (1974) in their study of baboons. It was found that, in half of the animals requiring large doses of nitroprusside, increasing metabolic acidosis heralded a fatal outcome. However, the smallest toxic dose in their baboons was equivalent to 320 mg h^{-1} in man, which is far in excess of normal clinical dosage. Lewis and others (1977) did not mention nitroprusside dosage or the equivalents in man. Neither did they relate their findings to clinical practice in man, although this relationship has been assumed by several authors since that time. Sodium nitroprusside has been used during pregnancy without apparent adverse effects on the fetus, as demonstrated by the two cases reported here and the previously reported case of Donchin and others (1978).

Note added in proof. Since we submitted this paper a further paper (Naulty, Cefalo and Lewis, 1981) has been published. This is a definitive article which describes a study similar to that of Lewis and others (1977) which has slightly different results. Eight near-term ewe preparations were studied, maternal arterial pressure being reduced by 20% for 1 h. In three of the ewes this was very easy, requiring sodium nitroprusside less than 1 $\mu g\,kg^{-1}\,min^{-1}$ and all mothers and fetuses did well. The other five required steadily increasing rates of SNP infusion (mean dose 25 $\mu g\,kg^{-1}\,min^{-1}$). All the fetuses died *in utero* within 30 min after cessation of the infusion although the mothers survived for another 60 min or more. Cyanide concentrations increased steeply in the non-survivor mothers and fetuses with umbilical artery concentrations being significantly greater than maternal arterial concentrations at 60 min. Significant metabolic acidosis developed in both mother and fetus in the non-survivor group.

The authors recommend that, if tachyphylaxis develops or more than $0.5\,\mu g\,kg^{-1}\,h^{-1}$ is being infused, the drug should be discontinued promptly. That dose is minute and so I am sure that the authors mean $0.5\,mg\,kg^{-1}\,h^{-1}$.

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UTILISATION DU NITROPRUSSIDE DE SODIUM POUR HYPOTENSION DELIBEREE AU COURS DE LA GROSSESSE

RESUME

On s'est servi de l'hypotension délibérée par le nitroprusside de sodium chez deux patientes enceintes san effets contraires apparents pour le fètus, afin de faciliter l'opération d'aneurismes cérébraux. La preuve de la nocivité du nitroprusside pour le fètus semble se fonder sur une expérience sur animaux dont les détails quant an dosage sont insuffisants.

VERWENDUNG VON NATRIUMNITROPRUSSID FÜR BEABSICHTIGTE HYPOTENSION WÄHREND DER SCHWANGERSCHAFT

ZUSAMMENFASSUNG

Beabsichtigte Hypotension durch Natriumnitroprussid wurde benutzt, um die Operation eines zerebralen Aneurysmas bei zwei Schwangeren zu erleichtern, ohne dass es zu erkennbaren schädlicHen Auswirkungen auf den Fötus gekommen wäre. Beweise dafür, dass Nitroprussid für den Fötus schädlich ist, scheinen sich aus einem einzigen Tierexperiment ergeben zu haben, für das keine ausreichenden Angaben über die Dosierung vorliegen.

USO DE NITROPRUSIDO DE SODIO PARA HIPOTENSIÓN INTENCIONAL DURANTE EL EMBARAZO

SUMARIO

Se usó la hipotensión intencional por nitroprusido de sodio con el fin de facilitar una operación quirúrgica en un aneurisma cerebral en dos pacientes embarazadas, sin que se observase efectos contrarios aparentes sobre el feto. La prueba de que el nitroprusido es dañino para el feto parece basarse en una experiencia animal para la cual se dieron detalles insuficientes en cuanto a la dósis.

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CONTINUOUS PAIN RELIEF FOR MULTIPLE FRACTURED RIBS

E. O'KELLY AND B. GARRY

SUMMARY

A technique for multiple intercostal nerve blocks using one intercostal injection is described. An indwelling catheter was placed in the intercostal space with the aid of a Tuohy needle. Injection through the catheter was used to obtain continuous analgesia extending over several intercostal segments in a patient with multiple fractured ribs.

Patients with fractured ribs admitted to an intensive care unit are in two categories: (a) multiple fractures with a flail segment; (b) one or more fractures but without a flail segment.

One of the latter group is described in this report. Usually these patients are treated in a general ward and are admitted to the intensive care unit when pain prevents coughing, deep breathing and bronchial toilette, causing atelectasis and pulmonary shunting of blood (Bendixen, Hedley-Whyte and Laver, 1963). Our method was prompted by the anatomical study of Nunn and Slavin (1980) which clearly demonstrated that there is relatively little resistance to flow of liquid upwards or downwards behind the parietal pleura once the posterior intercostal membrane is pierced. We have used a single injection of bupivacaine as a method of providing analgesia for a patient with fractured ribs but with a stable thoracic cage. The extent of pain relief achieved with bupivacaine injected at one interspace and the spread of the radio-opaque liquid injected subsequently further verifies their findings clinically.

CASE REPORT

A 67-yr-old man fell 2 m onto a wall and sustained fractures of the 6th, 7th, 8th, 9th and 10th left ribs and developed a left pneumothorax. He had a long history of moderate chronic obstructive airways disease and was a heavy smoker. He was admitted to a general ward where a chest drain was inserted and connected to an underwater seal. The pneumothorax lessened and x-ray on the evening of the first day revealed complete expansion of his lung. Pethidine 50 mg was given i.m. 4-hourly. His ability to tolerate breathing exercises, expectorate or even talk was severely impaired. During the following 48 h the patient's condition deteriorated with increasing dyspnoea, central cyanosis, agitation and mild confusion. Pa_{O_2} was 6.1 kPa when breathing air and a chest x-ray showed an expanded left lung with diffuse infiltration at the left base.

The patient was transferred to the intensive care unit. E.c.g., pulse and arterial pressure were monitored and remained relatively stable. The following procedure was then adopted: The patient sat upright with his legs over the edge of the bed in a comfortable position. Under aseptic conditions the skin was infiltrated with a local anaesthetic agent in the region of the angle of the 5th rib. A 19-gauge needle was advanced through the skin until the 5th rib was located. The needle was then "walked" to the lower edge of the ribs and advanced about 3 mm through the posterior intercostal membrane into the fifth intercostal space. Plain 0.5% bupivacaine 20 ml was injected and the needle withdrawn. The patient remained seated for a further 10 min and noticed marked pain relief. He was placed in a semi-recumbent position for a further 15 min when analgesia was complete from the 4th to the 9th segments, judged by pinprick and "springing" of fractured ribs. Increased skin warmth over the analgesic area was also noted. This single injection gave total pain relief for 8 h. During this period the patient was able to breathe deeply, talk more easily, became less confused and expectorated copious amounts of green sputum. Pa_{O_2} increased to 11.8 kPa (breathing 40% oxygen), allowing a reduction of FI_{O_2} to 0.30.

Then we inserted an indwelling catheter to enable administration of continuous regional analgesia. The patient was positioned and prepared as

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described and a Tuohy needle was introduced into the fifth intercostal space and 0.5% plain bupivacaine 10 ml was injected. A catheter was introduced through the needle with the bevel pointed medially and 2 cm introduced to the space. It was then left *in situ* and the needle withdrawn. The catheter was secured in place and a further 10 ml of 0.5% bupivacaine was injected after negative aspiration for blood. This provided excellent analgesia over the 4th to the 10th segments. To confirm the spread of bupivacaine we injected radio-opaque fluid through the cannula after first ensuring adequate analgesia. Meglumine lothalamate 10 ml was injected and an oblique x-ray taken after 15 min (fig. 1). The dye can be seen to spread over five spaces. A quantity of dye can be seen in the paravertebral space, indicating horizontal and vertical spread.

During the next 4 days, the patient's condition improved markedly, Pa_{O_2} remaining within the range 9.5–10.5 kPa with FI_{O_2} of 0.30, and his ability to co-operate with the physiotherapist resulted in expectoration of large quantities of sputum. He did not require systemic analgesic drugs during this period. The interval between injections was approximately 7–8 h and we continued to use 0.5% plain bupivacaine. On the 4th day we reduced the concentration to 0.25% plain, but continued to use the same volume (20 ml). The chest drain was removed after the 4th day and the intercostal cannula after the 6th day. On the 5th and 6th days the patient maintained Pa_{O_2} between 9.3 and 9.8 kPa, breathing air. The patient was discharged to the ward on the 7th day and left hospital a few days later.

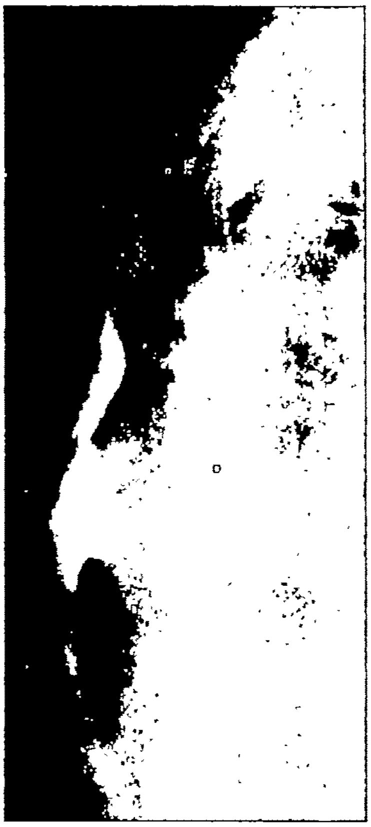

FIG. 1. Contrast material injected via catheter spreading in extrapleural tissue plane vertically and horizontally into the paravertebral area and along the thoracic aorta.

DISCUSSION

Pain related to respiratory movement is the principal problem in the patient with fractured ribs. This pain causes a reduction in respiratory excursion and thus increasing mismatch of ventilation and perfusion (Georg, Hornum and Mellemgaard, 1967) resulting in a decrease in arterial oxygen tension. The decrease in Pa_{O_2} in our patient was sufficient to cause symptoms of mild cerebral hypoxia. The limitation of respiratory excursion limits expectoration particularly in a heavy smoker with chronic obstructive airways disease and causes atelectasis and shunting. Our method of alleviating the pain was simple to perform and very acceptable to the patient. Multiple intercostal blocks cause discomfort to the patient and are time-consuming for the anaesthetist (Engberg, 1975).

We believe that the increased warmth of the skin over the anaesthetized area was a result of blockade of the sympathetic ganglia and chain caused by medial spread as shown in figure 1. Our patient developed no complications, the arterial pressure remaining stable after each injection; the total dose of bupivacaine was within the acceptable range.

The frequency of accidental pneumothorax during intercostal block is very low (Cronin and Davies, 1976).

We are confident that the spread of bupivacaine and radio-opaque fluid was not facilitated by any disruption of thoracic anatomy as a result of the patient's injury. The line of fractures corresponded roughly to the anterior axillary line and the site of our injection was at the angle of the rib—30 cm from the nearest fracture. It is unlikely that a correspondingly large area of pleura was disrupted on the postero–lateral chest wall, thus facilitating spread of solution. Furthermore, it would not explain the medial and consequent paravertebral spread as seen on the x-ray. We believe that the anatomy in this area was normal.

Theoretically, spread of anaesthesia to adjacent segments could occur via the extradural route as a communication exists between the intercostal space and the extradural space via the intervertebral foramen (Atkinson, Rushman and Lee, 1977). However, the x-ray demonstrates more direct spread in our patient.

We believe this method to be of value after thoractomy (Moore, 1975), cholecystectomy or upper abdominal surgery (Bartlett and Eastwood, 1952) and to merit further study.

ACKNOWLEDGEMENTS

We wish to thank Dr Padraic W. Keane, Director, Department of Anaesthesia and Professor James Murray, Department of Radiology, Regional Hospital, Galway for their help and advice. Thanks also to Mr Michael Maguire (photography), the Intensive Care Unit staff and Miss Regina Flannery for secretarial assistance.

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SOULAGEMENT CONTINU DE LA DOULEUR CAUSEE PAR DES FRACTURES MULTIPLES DES COTES

RESUME

On décrit dans cet article une technique permettant de bloquer de multiples nerfs intercostaux à l'aide d'une seule injection intercostale. On avait implanté un cathéter dans l'espace intercostal à l'aide d'une aiguille de Tuohy. L'injection effectuée à travers le cathéter a permis d'obtenir une analgésie continue s'étendant au-delà de plusieurs segments intercostaux d'un malade souffrant de fractures multiples des côtes.

ANHALTENDE SCHMERZENSLINDERUNG BEI MEHRFACHEN RIPPENBRÜCHEN

ZUSAMMENFASSUNG

Es wird eine Technik zur mehrfachen Interkostalnervenblockade mittels einer einzelnen interkostalen Injektion beschrieben. Ein Verweilkatheter wurde mittels einer Tuohy-Nadel in den Interkostalraum eingesetzt. Einspritzung durch den Katheter führte bei einem Patienten mit mehrfachen Rippenbrüchen zu einer anhaltenden Analgesie über mehreren Interkostalabschnitten.

ALIVIO CONTINUO DEL DOLOR PARA LAS COSTILLAS CON FACTURAS MULTIPLES

SUMARIO

Se describe una técnica para el bloqueo múltiple de los nervios intercostales, usando una inyección intercostal. Se colocó un cáteter en el interior del espacio intercostal con ayuda de una aguja Tuohy. La inyección a través del catéter se usó para obtener una analgesia continua a lo largo de varios segmentos intercostales en un paciente que sufría múltiples fracturas de costillas.

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MALIGNANT HYPERTHERMIA SYNDROME IN AN ANXIOUS PATIENT

R. FLETCHER, E. RANKLEV, A.-K. OLSSON AND S. LEANDER

SUMMARY

A 30-yr-old patient with fulminant ulcerative colitis was anaesthetized on three occasions, for colectomy and rectal stump removal. The first anaesthesia, with droperidol and fentanyl and pancuronium neuromuscular block, was uneventful. Addition of suxamethonium on the second occasion and use of the original drugs plus nitrous oxide for the third anaesthesia produced symptoms of MH, which was confirmed by muscle biopsy. There was no hyperthermia. The patient's admitted anxiety before the last two operations is believed to have played a role in the genesis of MH.

CASE REPORT

A 30-yr-old farmer (height 186 cm, weight 71 kg), in good health until 2 months previously, underwent colectomy during an episode of fulminant ulcerative colitis. Anaesthesia was induced with droperidol and fentanyl and neuromuscular block was effected with pancuronium. The lungs were ventilated with 65% nitrous oxide in oxygen (IPPV). The procedure was uneventful and the patient made a good recovery.

Six weeks later the patient was anaesthetized for removal of the rectal stump which showed inflammatory change. Anaesthesia was again induced with droperidol and fentanyl, followed by pancuronium 1 mg and suxamethonium 75 mg. Masseteric spasm developed immediately, and the heart rate increased from 90 to 160 beat min^{-1}. Two more doses of suxamethonium (25 mg and 50 mg) were given without the desired effect. The patient's forehead felt hot and the diagnosis of malignant hyperthermia (MH) was made. Tracheal intubation was performed with greater force than is usually necessary and the lungs were ventilated with 100% oxygen. Two litre of ice-cold fluid was infused i.v. and a urinary catheter inserted. Methylprednisolone 2 g, procaine 2 g and frusemide 40 mg were given. The rectal temperature after these measures was 37 °C and decreased thereafter.

A CO_2 Analyzer 930 (Olsson et al., 1980) showed a persistent carbon dioxide production of more than 400 ml min^{-1} with an end-tidal $P\text{CO}_2$ of about 4.5 kPa. Base excess was -1.0 and pH 7.39 after sodium bicarbonate 80 mmol had been given.

Ninety minutes after induction the patient was rouseable, and the rectal temperature was 36 °C. The trachea was extubated and the patient made a good recovery from anaesthesia. There was no muscle tenderness.

A muscle biopsy was later performed under local anaesthesia. *In vitro*, the muscle was initially stretched to 0.4 g. It showed an increase in basal tension of 0.6 g at 37 °C on exposure to 2% halothane. Caffeine 0.25 mmol litre^{-1} caused a further increase of basal tension of 0.5 g, and caffeine 0.5 mmol litre^{-1} a further 1.0 g increase (fig. 1).

The pathologist reported that in some areas the muscle had been completely replaced by connective tissue. There was pronounced muscle atrophy, with some vacuolar degeneration and internal placing of sarcolemma nuclei. There were cores in many muscle fibres. In some areas the features were those of collagenosis with vasculitis, in others the findings were typical of MH myopathy.

The patient was informed of this result and its implications. He was reassured that he need be in no danger from subsequent anaesthetics provided the anaesthetist was informed.

At the second attempt to excise the rectal stump, the anaesthetist was aware of the past history. The rectal temperature was 36.2 °C. Anaesthesia was induced with droperidol, fentanyl and

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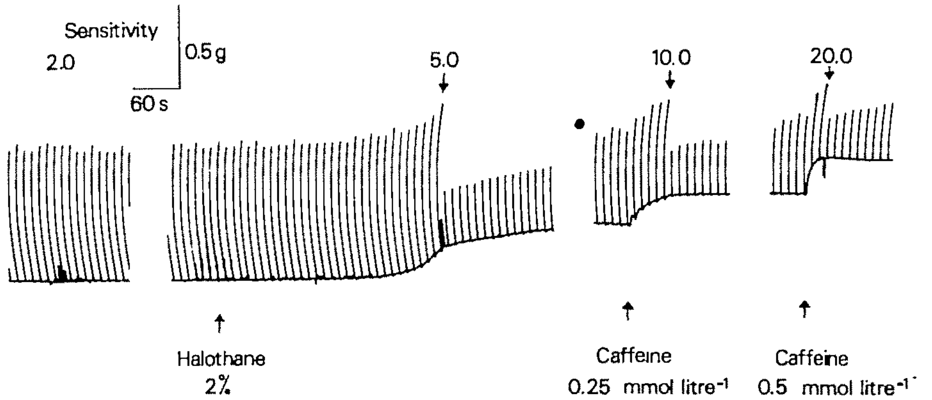

FIG. 1. Tracing obtained from *in vitro* muscle testing. The biopsy specimen, which was taken under procaine anaesthesia, was from vastus medialis, although not motor point. The upper arrows indicate changes in amplification of the force transducer signal. The basal tension is initially 0.4 g. Halothane 2% gave an increase of 0.6 g. Caffeine 0.25 and 0.5 mmol litre^{-1} in the perfusate gave further increases of 0.5 and 1.0 g respectively, in basal tension.

pancuronium. Tracheal intubation was easy. Ventilation of the lungs was with 65% nitrous oxide in oxygen. Almost immediately, the heart rate increased from 90 to 145 beat min^{-1}, $\dot{V}CO_2$ was 450 ml min^{-1} and end-tidal PCO_2 5.0 kPa. Ventilation (12 litre min^{-1}) was continued with 100% oxygen. As it seemed that the syndrome of MH was developing again, methylprednisolone, procaine and 1 litre of ice-cold Ringer acetate were given immediately i.v., after which the rectal temperature was 36 °C. Sodium bicarbonate 300 mmol was given i.v. At 40 min Pa_{CO_2} was 3.0 kPa, Pa_{O_2} 24.4 kPa, pH 7.495, base excess −4.0 mmol litre^{-1}.

The heart rate had decreased to 70 beat min^{-1} and $\dot{V}CO_2$ was 250 ml min^{-1} at 1 h. The operation continued. High lumbar extradural blockade was performed with the aim of blocking the adrenal innervation. The total anaesthetic time was 10 h. The lowest temperature recorded in the nasopharynx was 33.4 °C at 5.5 h. Thereafter it increased spontaneously to 36.5 °C during the 7-h abdomino-perineal operation. $\dot{V}CO_2$ was frequently increased in the presence of a normal end-tidal PCO_2 (mean of 16 observations: 280 ml min^{-1}). In the first 3 h after operation the heart rate was 140–160 beat min^{-1} although there was no hypovolaemia, and the nasopharyngeal temperature increased to 37.8°C.

DISCUSSION

There was no hyperthermia on either occasion when the diagnosis of MH was made. At the time of the second anaesthetic, the diagnosis was made on the grounds of masseter spasm after suxamethonium, increased heart rate and $\dot{V}CO_2$, and the *in vitro* response to halothane and caffeine (Ellis et al., 1978). Ice-cold fluids, steroids and procaine were injected without awaiting temperature measurement, which may explain the lack of hyperthermia.

At the third anaesthetic, the diagnosis was less clear. Induction was associated with a rapid increase in heart rate, which decreased only slowly and which could not be explained by difficult intubation. There must have been a large metabolic acidosis, since 300 mmol of bicarbonate was required to produce a base excess of −4.0 mmol litre^{-1}. In spite of the extradural anaesthesia, two surgical incisions, and the deliberate lack of any attempt to prevent heat loss, body temperature after and $\dot{V}CO_2$ during operation were unusually high in our experience, and suggest an increase in metabolism. This third anaesthetic may perhaps be regarded as an incomplete form of the MH syndrome. The condition was treated even more quickly than the previous occasion, since the anaesthetist was aware of the possibility. This, too, may explain the absence of hyperthermia.

We consider suxamethonium to have been the triggering agent in the second anaesthetic. For the third anaesthetic, droperidol, fentanyl, pancuronium and nitrous oxide were given. The first three drugs have been listed as suitable for MH-sensitive (MHS) patients (Cain and Ellis, 1977). The same authors regard the use of nitrous oxide as being justifiable in MHS patients, although it has been implicated (Ellis et al., 1974). It was continued throughout the operation, however, and is therefore less likely to have been responsible. There is a small possibility that the reaction was a result of pyrogens in one of the solutions given i.v. The reaction appears to have been too severe to be accounted for by the sympatheticomimetic properties of pancuronium. Pancuronium has been shown to afford partial protection against MH in pigs (Hall, Lucke and Lister, 1976) and Cain and Ellis (1977) believe that it may be used with caution in MHS patients.

The same drugs were used for the first and third anaesthetics. That they did not elicit the MH response at the first anaesthetic may be explained by the patient's (unsolicited) admission that whereas he was calm on the first occasion, he was very nervous before the second and third anaesthetics. Anxiety is believed to play an important role in the genesis of MH (Mogensen, Misfeldt and Hanel, 1974) and this may explain why some MH patients may previously not have reacted to known triggering agents. The part played by the extradural blockade is not clear. It was performed in the knowledge that, in the pig, MH can be prevented by adrenalectomy and treatment with bretylium (Lucke et al., 1978). At least it avoided the need for more muscle relaxants. Nevertheless, increased carbon dioxide production continued, suggesting that muscle metabolism had not returned to normal.

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SYNDROME DE L'HYPERTHERMIE MALIGNE CHEZ UN PATIENT ANXIEUX

RESUME

Un malade de trente ans souffrant d'une rectocolite ulcéro-hémorragique suraiguë a été anesthésié à trois reprises, pour une colectomie et pour l'ablation d'une excroissance rectale. La première anesthésie, par blocage neuromusculaire au dropéridol, fentanyl et pancuronium s'est passée normalement. L'addition de suxaméthonium pour la seconde opération et l'usage des produits originaux plus protoxyde d'azote pour la troisième anesthésie ont produit des symptômes de MH, qui ont été confirmés par une biopsie des muscles. Il n'y a pas eu d'hyperthermie. Le malade a reconnu qu'il était anxieux avant les deux dernières opérations, et on pense que ceci a pu jouer un rôle dans la génèse de la MH.

MALIGNES HYPERTHERMIE-SYNDROM BEI ÄNGSTLICHEM PATIENTEN

ZUSAMMENFASSUNG

Ein 30jähriger Patient mit fulminanter ulzerativer Kolitis wurde dreimal narkotisiert—für Kolonresektion und rektale Stumpfresektion. Die erste Narkose, mit Droperidol und Fentanyl und neuromuskulärem Pancuroniumblock, verlief ohne Zwischenfälle. Die Zufügung von Suxamethonium bei der 2 Narkose, und die Verwendung der ursprünglichen Drogen plus Stickoxyd für die 3 Narkose bewirkte Symptome oder Zeichen von MH, was durch Muskelbiopsie bestätigt wurde. Dies war aber keine Hyperthermie. Die vom Patienten angegebene Angst vor den beiden letzten Operationen dürfte dürfte eine Rolle in der Entstehung von MH-Symptomen gespielt haben.

SINDROME DE HIPOTERMIA MALIGNA EN UN PACIENTE CON ANSIEDAD

SUMARIO

Un paciente de 30 años de edad con colitis ulcerativa fulminante fue anestesiado en dos ocasiones para efectuar una colectomía y la extracción del muñón rectal. La primera anestesia, que se efectuó mediante droperidol, fetanilo y bloqueo neuromuscular por pancuronio, no presentó acontecimiento alguno. La incorporación del suxametonio en la segunda ocasión y el uso de la droga original más óxido nitroso para la tercera ocasión, produjo síntomas de MH, lo que se confirmó mediante la biópsia muscular. No tuvo lugar hipertermia alguna. El paciente admitió sufrir ansiedad antes de las dos últimas operaciones, lo que se cree jugó un papel en la génesis del MH.

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A SIMPLE AIR SAMPLING TECHNIQUE FOR MONITORING NITROUS OXIDE POLLUTION

J. C. AUSTIN, R. SHAW, D. MOYES AND P. E. CLEATON-JONES

SUMMARY

A simple, inexpensive device for the continuous low-flow sampling of air was devised to permit monitoring of pollution by gaseous anaesthetics. The device consisted of a water-filled Perspex cylinder in which a double-walled flexible-film gas sample collection bag was suspended. Air samples could be aspirated into the collection bag at flow rates of as low as 1 ml min^{-1} by allowing the water to drain from the cylinder at a controlled rate. The maintenance of sample integrity with aspiration and storage of samples of nitrous oxide in air at concentrations of 1000, 100 and 30 p.p.m. v/v was examined using gas chromatography. The sample bags retained a mean 94% of the nitrous oxide in air samples containing nitrous oxide 25 p.p.m. over a 72-h storage period.

Measures for decreasing occupational exposure to inhalation anaesthetics should be supported by the monitoring of air pollution to ensure that such measures are effective, and to enable an accidental leak of gas or malfunction in either scavenging equipment or ventilation system to be detected and corrected.

Ideally, monitoring should be carried out with air sampling devices which collect air samples on a continuous basis during the period of exposure. Intermittent snatch sampling is not suitable for routine monitoring purposes because the concentration of anaesthetic agent in the breathing zone of health personnel tends to fluctuate widely during induction and maintenance of anaesthesia. The continuous collection of the air sample enables the concentrations of pollutants in the sample to be expressed as a time-weighted average.

Several air sampling systems have been devised for collecting air samples on a continuous basis (Hallen, Ehrner-Samuel and Thomason, 1970; Corbett, 1973; Davenport et al., 1976; Whitcher and Piziali, 1977). Factors such as cost, convenience and sample volume have limited the adoption of these systems for general use.

Ideally, the equipment used to monitor air pollution should be inexpensive, simple, reliable and easy to operate. It should allow collection of air samples from the breathing zone of the anaesthetist or surgeon for periods extending over several hours. Air samples should be of relatively low volume for convenience of handling and carriage by post to a laboratory for analysis. Sample integrity should be maintained with minimal losses or extraneous contamination until analysis has been carried out (American Dental Association Council on Dental Materials and Devices, 1977).

The purpose of this paper is to report on the development and evaluation of a simple method for collecting air samples on a continuous basis to allow monitoring of nitrous oxide pollution in operating theatres and dental surgeries.

METHODS

Design considerations

To comply with the specifications for an ideal air sampling system, two criteria have to be met. First, restriction of the sample volume which is collected over periods extending up to 6 h and second, the maintenance of a consistent air sampling rate over the period of collection.

A previous study on snatch sampling techniques indicated that flexible nylon film gas sample bags retained air samples containing nitrous oxide with minimal losses for periods of up to 24 h after collection (Austin et al., 1978). These bags were used as prospective air sample containers for the development and testing of the equipment used in this study.

Sample collection can be carried out either by pumping or by aspirating air into these sample

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bags. Since mechanical pumps which will pump air at the required low flow rates of 1–5 ml min^{-1} are complicated and expensive to construct it was decided to collect air by means of an aspiration technique. Evacuated nylon sample bags were suspended in a rigid-walled water-filled container and by allowing the water to drain from the sealed container at the required rate an air sample was obtained. The air sample collection bag was provided with a nozzle which passed through the wall of the chamber. The end of the nozzle was provided with a silicone rubber septum seal. Air was aspirated into the bag by means of a hypodermic needle which was passed through the nozzle septum when air sampling was in progress (fig. 1).

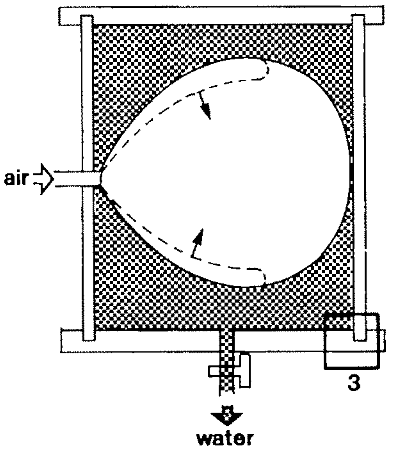

FIG. 1. Diagram to indicate the principle of the sampling device. As water runs out of the chamber the inner bag is expanded by air which is drawn into it. The seal between cylinder and baseplate (3) is enlarged in figure 3.

Pilot studies were carried out on the system of sampling using a 0.5-litre nylon bag. However, it was found that the nylon bag alone was unsuitable; the nylon film, being hygroscopic, absorbed water. After several hours of immersion gas chromatography showed that the water vapour concentration had increased in air samples collected in the bags, indicating that the nylon film was pervious to water vapour. This problem was overcome by enclosing the nylon sampling bag in an outer protective sleeve of high density polyethylene. This measure prevented water from coming into direct contact with the nylon sampling bag.

Construction of gas sample bags

The inner nylon bags were made of 150 mm wide × 0.05 mm thick tubular nylon film (Nylon 6—fusion point 218 °C, Portex, Hythe, Kent). The tubular film was cut into 190 mm lengths to construct sample bags with a capacity of approximately 650 ml of air when the open ends had been sealed. The outer sleeves of the sample bags were made of 210 mm lengths of 162 mm wide × 0.125 mm thickness tubular high density polyethylene (HDPE) film (Allied 3204, Keagrams (Pty) Ltd, Aeroton, South Africa).

One end of the tubular nylon and HDPE film was heat-sealed and the nylon film was inserted inside the HDPE sleeve thus formed. A 12 mm diameter hole was punched through the two layers of film to make provision for the insertion of a specially constructed brass nozzle, the lumen of which provided a connection between the inner nylon gas sampling bag and the environment to be sampled. The brass nozzle was turned from 19 mm hexagon brass, and consisted of a 12 mm diameter threaded stem with a hexagonal head at one end. An axially positioned hole was bored through the nozzle and the threaded end was counterbored and tapped to provide a recess for accommodating a 3 mm thick silicone rubber septum which was held in position with a grub screw (fig. 2).

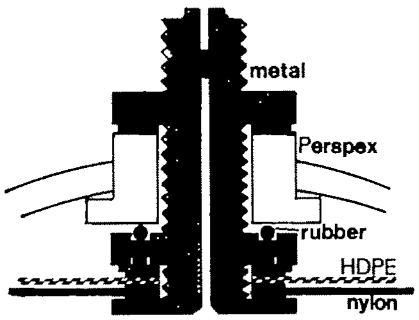

FIG. 2. Details of the various components of the sampling nozzle attachment to the double-walled sampling bag and Perspex chamber. HDPE / high density polyethylene.

In assembling the sample bags, this nozzle was inserted through the nylon and HDPE films from the lumen of the inner bag. Silicone rubber gaskets, 1 mm thick, were interposed between the base flange of the nozzle and the nylon film, between the nylon film and HDPE film and between the HDPE film and a metal washer which was clamped down under a securing nut. The securing nut had "O" rings positioned in recesses in both its upper and lower face to prevent water leaking from the chamber along the threaded nozzle stem or at the point at which the nozzle passed through the chamber wall (fig. 2).

After the nozzle had been fixed in position, the remaining open ends of the nylon and HDPE films were in turn heat-sealed to form the inner sample bag and outer protective bag. The silicone rubber septum was positioned in the recess at the end of the sampling nozzle, the inner bag was inflated with approximately 250 ml of air and the whole unit was submerged in water for several hours to test for air and water leaks. Leaking bags were discarded. Bags which did not leak were evacuated by aspirating residual air from the bags with a hyperdermic needle connected to a high vacuum pump (Speedivac, Edwards, Crawley, Sussex) and stored until they were required for use.

Construction of the water chamber

The water chamber was constructed of clear acrylic (Perspex AECI, Johannesburg). The body of the chamber was made of a 210 mm length of 150 mm diameter acrylic tubing and the ends of 175 mm diameter discs of 12 mm thick acrylic sheet. The ends of the tube were accurately faced on a lathe and fitted into stepped circular recesses machined in one face of the end plates. These recesses were provided with an "O" ring seal (fig. 3). The end-plates were held on to the body of the chamber with four tie rods. The upper end-plate of the chamber was fitted with a dual-purpose filling and draining nozzle and an air vent to allow air to escape during filling. Provision was made for the sampling bag nozzle to pass through an opening in the side wall of the chamber. An acrylic collar was cemented in the curved wall of the chamber to provide a flat face for seating the "O" ring seal in the upper face of the nut positioned on the nozzle of the sample collection bags.

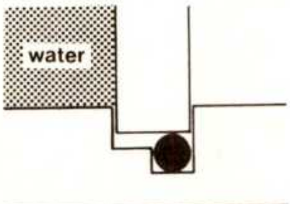

FIG. 3. Diagram of the seal between base plate and chamber wall to show the sealing "O" ring.

Preparation of the chamber for air sampling

The sample bag was placed in the body of the chamber and the nozzle was passed through the collar in the chamber wall and secured with a nut. The ends of the chamber were seated on the body and fastened by means of wing nuts which were screwed onto the tie rods. The chamber was inverted and filled with water via the filling and drainage nozzle. All air was vented from the chamber via a vent hole positioned on the periphery of the junction between the body and base of the chamber. The filling nozzle was then sealed with a silicone rubber septum which was held in position with a threaded septum cap.

Sampling procedure

The chamber was suspended from an i.v. fluid stand and an i.v. infusion set with its drip chamber and plastic tubing primed with water connected to the lower drainage nozzle (figs 4, 5). A gas sampling needle was passed through the septum of the sampling bag, so that air could be aspirated into the sample bag by opening the roller clamp on the infusion set and allowing water to drain from the chamber. The rate of flow of water from the chamber determines the rate of air aspiration and sampling. Once the flow rate is set it was found that

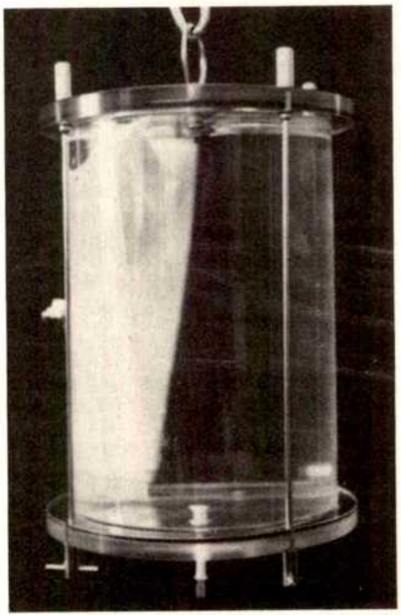

FIG. 4. Assembled sampling device suspended from a drip stand.

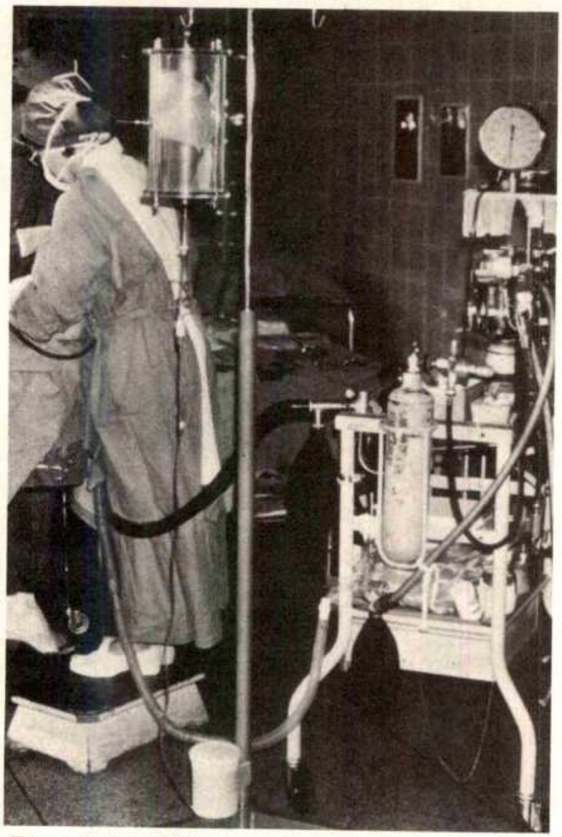

FIG. 5. The sampling device in use during an operation.

it remained constant for the period of sampling without further adjustment being necessary. The drip chamber provides a visual means of monitoring the rate of sample collection during the period of gas sampling. Adhesion between the opposed walls of the evacuated nylon sample bag during atmospheric sampling was not found to be a problem because, in spite of vacuum aspiration, the nylon film adjacent to the nozzle was always kept slightly parted by the protrusion of the base flange of the metal nozzle into the bag. Cleavage of the opposed nylon surfaces began as soon as the gas sampling needle was inserted through the sample bag septum and drainage of water from the chamber commenced.

Evaluation of the air sampling system

The air sampling system was tested to determine if it would reliably aspirate air samples at a constant flow for several hours and to determine if losses of nitrous oxide occurred when air containing trace concentrations of nitrous oxide was aspirated into the sample bag using the water displacement method and the bag removed from the chamber and stored for up to 72 h.

The first part of the evaluation was confined to estimating the constancy of the sampling rate and the losses of nitrous oxide which occurred when air with a known concentration of nitrous oxide was transferred from stock sample bags to the sample collection bags using the aspiration technique. Stock samples of nitrous oxide in air were prepared in 3.5-litre capacity nylon film bags (Austin et al., 1978). The nylon bags were inflated with dry air from a compressed air cylinder (Afrox, Germiston, South Africa). Medical grade nitrous oxide was added to the bags in volumes of approximately 3.5 ml, 0.35 ml and 0.11 ml to give concentrations of approximately 1000 p.p.m., 100 p.p.m. and 30 p.p.m. (v/v) respectively. These concentrations were selected on the basis of a previous study on nitrous oxide pollution in dental surgeries, in which this range of concentrations was shown to occur (Cleaton-Jones et al., 1978).

After each stock sample had been prepared, the concentrations of nitrous oxide in air were determined with a Pye Unicam Model GCV gas chromatograph. Nitrous oxide was separated using a 2 m × 4 mm borosilicate glass column packed with 80–100 mesh Poropak Type Q (Waters Assoc., Milford, Massachusetts, U.S.A.) at a column temperature of 80 °C. Helium was used as a carrier gas at a flow rate of 25 ml min^{-1}. Nitrous oxide was detected with a katharometer, the filament temperature being 180 °C and the detector oven temperature set at 100 °C. The injection port temperature was 150 °C. Peak areas were integrated with a Pye DP 88 integrating computer and compared with the peak areas obtained with commercially prepared 1000-p.p.m. and 100-p.p.m. (v/v) nitrous oxide in nitrogen standards (Altec Associates Calibration Gas, Arlington Heights, Illinois, U.S.A.). All the concentration-prepared bulk samples were within 10% of the desired 1000-p.p.m. and 100-p.p.m. and within 25% of the desired 30-p.p.m. concentrations of nitrous oxide in air.

Ten prepared bulk samples of nitrous oxide in air at concentrations of ±10% of 1000 p.p.m., 100 p.p.m. and 25% of 30 p.p.m. (v/v) were, in turn, suspended next to the sampling chamber and connected to the collecting bags in the acrylic chambers by means of a 21-gauge stainless steel cannula. Approximately 0.5 litre of air was aspirated from the bulk sample bags into the nylon collection bags by the water displacement collection technique using a flow rate of 4 ml min^{-1} over a 2-h period of collection.

The concentrations of nitrous oxide in air in the bulk sample bags prepared at the three different concentrations were determined by gas chromatography just before sampling was begun and 24 h thereafter. The concentration of nitrous oxide in air in the sample collection bags was similarly determined immediately after the 2-h sample collection period and 24 h later. The concentrations of nitrous oxide in the aspirated air sample at the end of the sampling procedure and 24 h later were expressed as percentages of the original concentrations of nitrous oxide in the bulk samples from which they originated. This provided a measure of nitrous oxide losses associated with the aspiration and storage phases of the exercise. Differences in mean concentrations of nitrous oxide in air between the three groups of bulk sample bags and their corresponding sample collection bags immediately after collection and 24 h later were examined statistically using the paired *t* test.

To determine the retention of nitrous oxide in the sampling bags over a 72-h period, eight bulk samples of nitrous oxide in air were prepared by adding nitrous oxide 0.09 ml to approximately 3.4 litre of air to provide air samples containing approximately 25 p.p.m. (v/v) of nitrous oxide in air. The concentrations of nitrous oxide were determined by gas chromatography and adjusted, if necessary, so that they were between 20 and 30 p.p.m.

Eight loose gas sampling bags were then, in turn, connected directly to these eight bulk sample bags by means of 21-gauge stainless steel cannula and approximately 250 ml of air transferred from the larger to the smaller bags by lightly squeezing the larger bag. This procedure was a direct gas transfer between the bulk sample and sample collection bag. It was carried out with the sample collection bags removed from the Perspex water chamber. The bulk sample bags were then disconnected and the concentrations of nitrous oxide in air in the eight collection bags were determined by means of gas chromatography immediately after gas transfer and at intervals of 24, 48 and 72 h thereafter. The retention of nitrous oxide recorded at each time interval was expressed as the percentage of the initial concentration of nitrous oxide in the sample bag immediately after it had been partially filled.

RESULTS

The concentrations of nitrous oxide in the samples of air collected by means of the water displacement–sample aspiration method immediately after sample collection and 24 h later at the three concentrations selected for this study are detailed in table I.

At the three concentrations of nitrous oxide in air tested (1000, 100 and 30 p.p.m.) the slow transfer of the air sample resulted in losses of less than 1.5% at the two higher concentrations and less than 4% at the lowest concentration, 30 p.p.m. The latter value was equivalent to nitrous oxide 1.2 p.p.m. in air. Twenty-four hours later further significant losses of nitrous oxide were recorded in the two groups of sample bags at the 1000- and 100-p.p.m. concentrations of nitrous oxide ($P < 0.01$). These losses were, however, very small, being a mean 1.7% and 0.6% respectively. At the lowest concentrations of 30 p.p.m. a slight mean increase of nitrous oxide of 1.7% was recorded.

TABLE I. *Mean concentration of nitrous oxide in air expressed as a percentage of the concentration of nitrous oxide in the air samples from which it was collected.* *(*Range in parentheses*)

Group	Initial concn N_2O in bulk sample bags (p.p.m. v/v ± SD = 100%) ($n = 10$)	N_2O immediately after sample collection (% ± SD)	N_2O 24 h after sample collection (% ± SD)
1000 p.p.m.	1045 ± 59 (880–1103)*	98.6 ± 1.7	96.9 ± 2.6
100 p.p.m.	104 ± 10 (92–118)	98.5 ± 2.2	97.9 ± 1.6
30 p.p.m.	32.3 ± 3 (25–36)	96.1 ± 7.0	97.8 ± 3.9

The differences between the mean concentrations of nitrous oxide in air in the bulk sample bags and their corresponding sample collection bags immediately after collection and 24 h later are detailed in table II.

TABLE II. *Analyses of the differences between the mean concentrations of nitrous oxide in air in the initial bulk samples and the aspirated samples immediately after collection and 24 h later. BS = bulk sample; AS = aspirated sample; n.s. = not significant.*

Group	Differences in N_2O concentration	t value	Significance
1000 p.p.m.	BS *v.* AS 0 h	0.64	n.s.
	AS 0 h *v.* AS 24 h	1.75	n.s.
	BS *v.* AS 24 h	3.61	$P<0.01$
100 p.p.m.	BS *v.* AS 0 h	2.06	n.s.
	AS 0 h *v.* AS 24 h	0.7	n.s.
	BS *v.* AS 24 h	3.6	$P<0.01$
30 p.p.m.	BS *v.* AS 0 h	1.58	n.s.
	AS 0 h *v.* AS 24 h	0.03	n.s.
	BS *v.* AS 24 h	1.68	n.s.

The mean percentage of nitrous oxide retained by the eight loose sample bags at 24, 48 and 72 h after filling with air containing approximately 25 p.p.m. v/v of nitrous oxide in air by the manual inflation transfer technique are detailed in table III.

TABLE III. *Mean concentration of nitrous oxide in air expressed as a percentage of the concentration of nitrous oxide in the sample bags at various intervals after filling*

Sample	Concentration (%)
Initial concentration N_2O in sample bags p.p.m. v/v±SD = 100%) ($n = 8$)	25.3±2.9 (range = 23–30)
24 h	95.0±6.0
48 h	92.0±5.5
72 h	94.0±7.4

Twenty-four hours after transfer of the eight air samples containing ±25 p.p.m. of nitrous oxide in air, there was a mean loss of 5% of nitrous oxide in the sample. A further mean 3% of the nitrous oxide was lost in the next 24 h and at 72 h the mean concentration of nitrous oxide in the air in the sample bags was 94% of the original concentration. This result reflected a 2% increase over the mean 48 h concentration. At the mean concentration of 25 p.p.m. v/v of nitrous oxide in air, this was equivalent to a 2 p.p.m. increase. This slight discrepancy can be attributed to the accuracy limitations of nitrous oxide detection of the gas chromatograph at the low concentration selected to determine the loss of nitrous oxide from the sample bags.

DISCUSSION

The simple continuous sampling method which has been devised will provide a convenient and low-cost method for routinely monitoring nitrous oxide pollution in operating theatres and dental surgeries. The method meets all the requirements for an air sampling system laid down by the American Dental Association's Council on Dental Materials and Devices (1977). The mean losses of nitrous oxide which occurred with the collection of the air sample and its storage for 24 and 72 h at the lowest concentration tested (30 and 25 p.p.m. v/v) were less than 6% of the mean concentration of nitrous oxide present in the prepared bulk samples. At these concentrations the loss represented 1.8 p.p.m. v/v of nitrous oxide in air which is considered to be a neglible loss in an air pollution monitoring procedure. This method of sampling has been used routinely in our laboratory for more than 18 months since it was devised. It has been found to be reliable in the hands of both our staff and those of lay personnel who have operated the equipment on our behalf in a survey of nitrous oxide pollution which is being conducted in operating theatres in hospitals in Johannesburg.

ACKNOWLEDGEMENTS

The authors are most grateful for the accurate typing of the manuscript by Mrs J. Long and for the photographic assistance of Mrs E. Pain.

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METHODE SIMPLE D'ECHANTILLONNAGE DE L'AIR POUR SURVEILLER LA POLLUTION PAR LE PROTOXYDE D'AZOTE

RESUME

Il vient d'être mis au point un dispositif simple et peu onéreux permettant l'échantillonnage en continu et à faible débit de l'air, afin de surveiller la pollution par les gaz anesthésiants. L'appareil se compose d'un cylindre en Perspex rempli d'eau dans lequel est suspendu un sac à double paroi et en pellicule flexible servant à la collecte des échantillons de gaz. Les échantillons d'air peuvent être aspirés dans le sac de collecte à des débits aussi faibles que 1 ml min^{-1}, en laissant s'écouler l'eau du cylindre à un débit contrôle. Le maintien de l'intégrité de l'échantillon, l'aspiration et l'entreposage des échantillons de protoxyde d'azote dans l'air à des concentrations de 1000, 100 et 30 p.p.m. v/v ont été surveillés par chromatographie en phase gazeuse. Les sacs d'échantillons ont retenu en moyenne 94% du protoxyde d'azote des échantillons d'air contenant 25 p.p.m. de protoxyde d'azote, pendant une durée d'entreposage de 72 h.

EINE EINFACHE LUFTPROBENENTNAHME TECHNIK ZUR ÜBERWACHUNG VON STICKOXYDULVERUNREINIGUNG

ZUSAMMENFASSUNG

Eine einfache, billige Vorrichtung zur kontinuierlichen Luftprobenentnahme bei schwachen Flussraten wurde entwickelt, um eine Überwachung von Verunreinigungen durch gashaltige Narkosemittel zu ermöglichen. Diese Vorrichtung bestand aus einem mit Wasser gefüllten Perspexzylinder, in dem ein doppelwändiger, flexibler Gassammelbeutel aufgehängt wird. Luftproben konnten sogar bei niedrigen Flussraten von 1 ml min^{-1} in den Sammelbeutel eingesaugt werden, indem man das Wasser zu einer kontrollierten Rate aus dem Zylinder fliessen lässt. Die Aufrechterhaltung von Probenintegrität bei der Einsaugung und die Aufbewahrung von Stickoxydulproben in Luft bei Konzentration von 1000, 100 und 30 p.p.m. V/V wurde mittels Gaschromatographie untersucht. Die Probebeutel behielten im Mittel 94% des Stickoxydul in Luftproben mit 25 p.p.m. Stickoxydul über eine Aufbewahrungsperiode von 72 Stunden.

TECNICA SENCILLA PARA EL MUESTREO DE AIRE DESTINADA A LA VIGILANCIA DE LA POLUCION MOTIVADA POR OXIDO NITROSO

SUMARIO

Se construyó un dispositivo sencillo y barato para llevar a cabo el muestreo de aire, mediante circulación lenta y continua, para que fuera posible la vigilancia de la polución ocasionada por los elementos anestésicos gaseosos. El dispositivo consistio de un cilindro de Perspex lleno de agua en el que se suspendió una bolsa de doble pared de película flexible destinada a la recogida de muestras gaseosas. Las muestras de aire pudieron aspirarse hasta la bolsa de recogida con regimenes de flujo tan bajos como de 1 ml min^{-1}, al permitir que el agua purgara desde el cilindro a un ritmo controlado. Se examinó mantenimiento de la integridad de las muestras, con aspiración y almacenamiento de muestras de óxido nitroso en el aire, a concentraciones de 1,000, 100 y 30 p.p.m. v/v, haciendo uso de cromatología de gases. Las bolsas de muestreo retuvieron una media de 94% de óxido nitroso en las muestras de aire que presentaban 25 p.p.m. de óxido nitroso, por espacio de 72 horas de almacenamiento.

Br. J. Anaesth. (1981), **53**, 1005

CORRESPONDENCE

LUMBAR EXTRADURAL ANALGESIA

Sir,—I would like to suggest a further theory for failure of lumbar extradual analgesia, having read a recent letter from Professor Downing (1981), and with reference to Sharrock (1979).

An 82-yr-old man presented for surgery as an emergency with symptoms and signs of a large bowel obstruction. A previous history of congestive cardiac failure, emphysema and cor pulmonale were regarded as indications for extra- or intradural anaesthesia. The patient was thin and was dehydrated, with a blood urea concentration of 30 mmol litre^{-1}, although slow rehydration, having regard to incipient cardiac failure, had taken place since that measurement. With the patient in the lateral position an 18-gauge Tuohy needle was inserted at the L3/L4 position and to a depth of 5 cm; having used the loss of resistance test a catheter was inserted with ease. Bupivacaine 0.5%, 8 ml was injected with no effect. A second extradural puncture was performed at L4/L5, with a definite loss of resistance at 6 cm, and again a catheter was inserted with ease. Twelve millilitre of 0.5% bupivacaine was injected; slight patchy analgesia on pinprick testing resulted. Following this, a 22-gauge spinal needle was passed at L4/L5, L3/L4 and L2/L3, but no cerebrospinal fluid could be withdrawn.

Is it possible that severely dehydrated patients have less cerebrospinal fluid, with resulting shrinkage of the spinal canal and a compensatory expansion of the extradural space? This may explain the slight patchy analgesia with conventional volumes of bupivacaine and the inability to elicit the spinal canal. Perhaps this type of patient should be placed in a sitting position for extra- or intradural anaesthetic techniques.

A. L. Gillies
Glasgow

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INTEGRATED PERSONAL SAMPLING SYSTEM

Sir,—We agree with the findings of Campbell and his colleagues (1980) that the commercial prototypes of our sampling devices can give erroneous results. We carried out laboratory studies (Davenport, Halsey and Bateman, 1980) and in some cases found it necessary to modify the equipment before its use in our regional survey of operating theatres, during which, of course, we constantly checked its correct functioning.

We have informed the manufacturers of the faults, but we would be grateful to hear from others of any malfunctions or practical problems in its use as a method of measuring operating room pollution.

H. T. Davenport
M. J. Halsey
B. M. Wright
Harrow, Middlesex

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ADVERSE RESPONSES TO I.V. ANAESTHETICS

Sir,—Drs Beamish and Brown (1981) found that the overall frequency of adverse responses to Althesin was 1 in 608 administrations. Scott (1979) reported a frequency of 1 in 430 reactions following Althesin and other estimates have ranged from 1 in 900 (Evans and Keogh, 1977) to 1 in 11 000 (Clarke et al., 1975).

I have been using Althesin for about 10 years and I have encountered only two adverse reactions in 1972 (Mehta, 1973). Both patients were aged less than 25 yr and exhibited severe hypotension and a generalized rash soon after the administration of Althesin. Since then I have diluted Althesin with equal volume of normal saline or water, using a 23-gauge needle for injection. Both these measures ensure that the drug is injected slowly. I administer Althesin over a period of 60 s and do not avoid this drug in patients with a history of atopy, allergy, hypersensitivity reactions or asthma and have received Althesin on previous occasions. Since 1972 I have administered Althesin to approximately 6000 patients and I have not seen any adverse reaction to this i.v. agent.

Perhaps the increase in plasma histamine concentration following Althesin, which is involved in the production of hypersensitivity reactions and is caused either by direct pharmacological effect or by activation of the classical and alternate pathway for the conversion of compliment C3, depends on the rate at which this drug is introduced into the circulation. It is highly likely that many of the adverse reactions reported by Drs Beamish and Brown represent over-dosage either in the absolute sense or in the relative sense, by which I mean the correct dose given too fast.

S. Mehta
Burnley

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Sir,—Dr Mehta has suggested that many of the adverse reactions to i.v. anaesthetic agents reported by us (Beamish and Brown, 1981) represent over-dosage of the agent leading to direct release of histamine, or activation of the complement pathway. Eight of the 13 patients received less than the recommended dose of Althesin (0.05 ml/kg body wt) and the remaining five received within 0.5 ml of the correct dose. Thus none of these reactions to Althesin can be described as over-dosage in the absolute sense.

We have no records of how fast the Althesin was administered to our patients and are therefore unable to add to Dr Mehta's observations about rate of injection. The freedom from reactions with his technique is impressive. Perhaps a dilute preparation of Althesin should be marketed instead of the existing concentrate.

D. Beamish
D. T. Brown
Edinburgh

PHYSOSTIGMINE ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION

Sir,— We were interested to read the article on physostigmine antagonism of morphine-induced respiratory depression in dogs and rabbits (Weinstock et al., 1980). Physostigmine salicylate has been used in adult patients in this unit for a number of years, primarily to reverse the effect of hyoscine supplementation of total i.v. anaesthesia incorporating morphine 4.5 mg kg^{-1} (May, Machin and Wyatt, 1978).

The awakening effect is quite remarkable but, as Dr Weinstock described, repeated doses of physostigmine may be needed. If the condition of the patient permits, it is possible to wean patients from artifical ventilation soon after completion of surgery, antagonizing with atropine, neostigmine and physostigmine. In a previously unpublished series using a similar dose of morphine with no hyoscine supplement, tracheal extubation was also possible with reversal in the normal fashion without physostigmine. This is probably a result of the pharmacokinetics of morphine following cardiopulmonary bypass, during which dilution with a large volume of crystalloid fluid and a diuresis with increased morphine excretion occurs.

We feel that the findings presented in this article show that, rather than a specific narcotic antagonist effect, physostigmine acts as a non-specific analeptic. It is a pity that no control group, given physostigmine alone, was included in Dr Weinstock's study to clarify this point. We agree with his implication that, in clinical anaesthesia, the use of conventional narcotic antagonists is far from satisfactory and should be avoided where possible, but feel that the place for physostigmine in the anaesthetists' armamentarium is already filled by doxapram.

In our experience with physostigmine in adults the dose is approximately 0.07 mg kg^{-1}, compared with Dr Weinstock's dose of 0.1 mg kg^{-1}. Repeated doses in this range, which may be necessary because of the short duration of action of physostigmine, may lead to problems with neuromuscular transmission.

It would be difficult to find a better description of the pharmacology of physostigmine in these respects than the delightful original description by Christison (1855) who heroically administered the drug to himself: "Having ascertained the mode of death from the action of the ordeal-bean, I did not consider it advisable to study further the details of its action by means of experiments on animals [rabbits] because I had been fully informed as to this in a more precise manner by an experiment made with the bean in my person. . . . I carefully chewed and swallowed the fourth of a seed, which originally weighed forty-eight grains. A slight giddiness which occurred in fifteen minutes, was ascribed to the force of imagination; and I proceeded to take a warm shower bath . . . . My mental faculties [were] quite entire, . . . the mind was so active all the while, . . . I could not vomit. The abdominal muscles acted too feebly; . . . twitches across the pectoral muscles."

P. C. W. Hunt
R. Wyatt
Leicester

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NEOSTIGMINE AND TUBOCURARINE NEUROMUSCULAR BLOCK

Sir,—I read with great interest the report of Feldman and Agoston (1980) showing that, in the isolated arm, neostigmine fails to modify the development of neuromuscular block in the presence of a high local concentration of tubocurarine. Only when the tourniquet was released and the concentration of tubocurarine was reduced did neostigmine increase the rate of recovery from the action of non-depolarizing block. The report confirms the findings of Baraka (1967, 1977) that neostigmine cannot antagonize an overdose of tubocurarine, and is in agreement with my contention that the majority of cases of irreversible curarization are a result of high concentration of drug in the plasma.

The report has suggested also that neostigmine fails to prevent the development or modify the extent of the neuromuscular block produced by subparalytic concentrations of tubocurarine. Also, it has suggested that, unless a suitable gradient exists between the receptor and the plasma, allowing drug molecules to leave the receptor area after they have been displaced from the receptor site, it will be impossible to antagonize the neuromuscular block even with large doses of neostigmine. These findings may apply to the isolated arm technique, but do not apply to other preparations such as the isolated phrenic nerve–diaphragm preparation of the albino rat with which I have repetitively shown that neostigmine can reverse completely the neuromuscular block achieved by adding a fixed concentration of tubocurarine to the perfusion bath. Also, prior addition of the same dose of neostigmine could prevent the development of neuromuscular block (Baraka, 1961). I have confirmed these findings in man (fig. 1), demonstrating that prior administration of neostigmine can prevent the neuromuscular blocking effect of a subsequent injection of tubocurarine. A three-fold increase in the dose of tubocurarine was required to produce neuromuscular block in the presence of neostigmine.

These different results can be attributed to the different experimental techniques. The isolation of the arm by a tourniquet may induce transient hypoxia at the neuromuscular junction, and hence neostigmine might be effective only after release of the tourniquet. During my study on the isolated phrenic nerve–diaphragm preparation, I have observed that, whenever hypoxia is allowed (by interrupting the oxygen flow to the perfusion bath), fatigue of the preparation rapidly occurs, tubocurarine block is potentiated and neostigmine fails to achieve reversal of the neuromuscular block. The resumption of oxygenation is followed by recovery of neuromuscular transmission. Acetylcholine synthesis and release are energy dependent. Also, the depolarization–repolarization sequence associated with neuromuscular transmission requires relatively large amounts of energy in excess of that necessary to maintain resting conditions. It is possible that hypoxia or fatigue of the neuromuscular junction, or both, can potentiate curare block and contribute to irreversible curarization.

Waser (1967) has shown in mouse diaphragm autoradiographs, that the radioactivity in the endplates following the administration of labelled curarine (^{14}C-calabash curarine) is not noticeably diminished when the neuromuscular block is reversed with neostigmine. I have observed in man that tubocurarine plasma concentrations at different intervals following i.v. injection do not differ significantly whether or not the block has been reversed with neostigmine (Baraka, unpublished work). These studies suggest that neostigmine can produce effective reversal without displacement of the curare molecules from the receptors. The acetylcholine accumulating at the endplate following neostigmine, probably acts on the curare-free cholinergic receptors. That is why an overdose of curare blocking all the cholinergic receptors cannot be reversed effectively irrespective of the dose of neostigmine used.

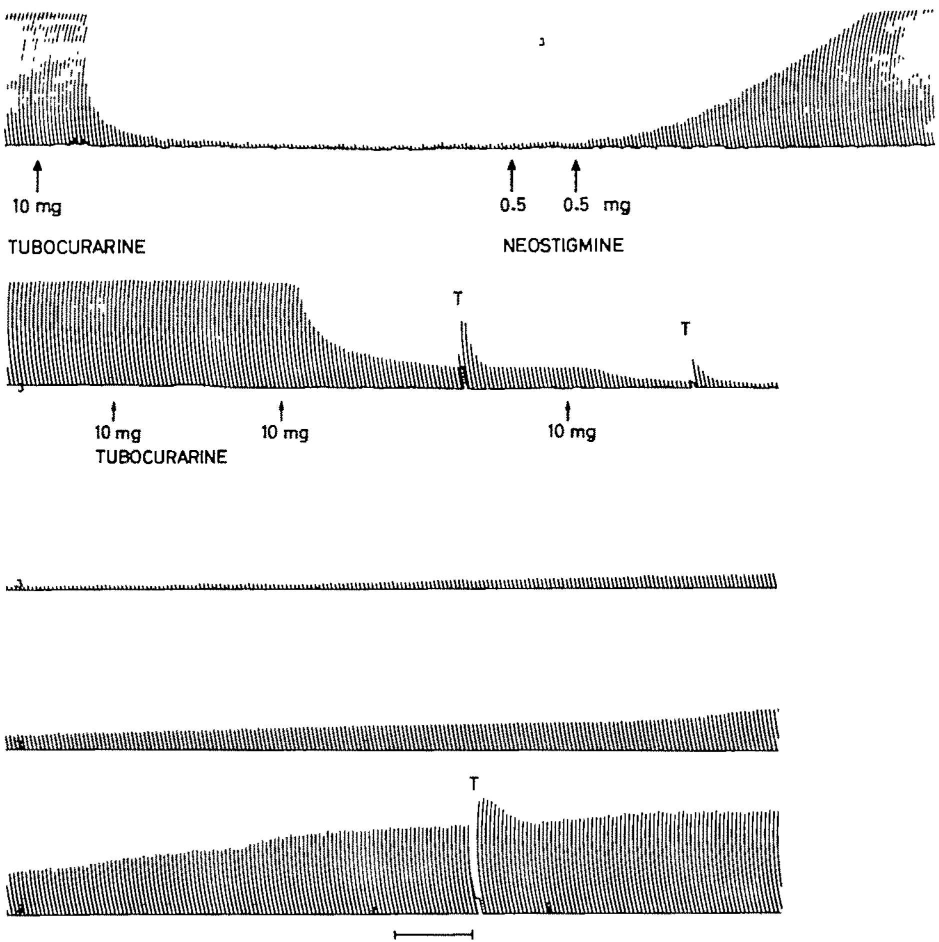

FIG. 1. Top trace: Twitch response to ulnar nerve stimulation at 4-s intervals. Tubocurarine 10 mg i.v. produced complete neuromuscular block readily reversed by neostigmine. Remaining traces: Twitch response to ulnar nerve stimulation at 4-s intervals in another patient. Tubocurarine was injected 5 min after a prior injection of neostigmine 0.05 mg kg^{-1}. Tubocurarine 10 mg did not produce any neuromuscular block. Additional doses of tubocurarine up to 30 mg were required to achieve about 95% block.

Certainly, a suitable gradient existing between the receptors and the plasma following redistribution and elimination of the relaxant, will allow the relaxant molecules to leave the receptor area, and hence ensures a more rapid rate of recovery from neuromuscular block, and avoids "recurarization" after an effective reversal has been achieved.

ANIS BARAKA
Beirut, Lebanon

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Sir,—Dr Baraka raises two separate points.

(1) Whether neuromuscular block can be successfully reversed by neostigmine in the presence of a high plasma concentration of tubocurarine. We have demonstrated this is not possible in the isolated arm, which is in agreement with the clinical findings of many anaesthetists, including Dr Baraka. We have also found that one can antagonize neuromuscular block by neostigmine or carbachol in the presence of tubocurarine in the water bath of the rat phrenic nerve preparation. Since one cannot reverse the block in man in similar circumstances using either the isolated arm or the whole patient, this suggests that the pharmacodynamics of the animal preparation are not a suitable model for what happens *in vivo*.

(2) Dr Baraka reports his experience that pretreatment with neostigmine increases the dose of tubocurarine required to produce neuromuscular block. Unfortunately I can think of no circumstance in which I would wish to administer a large dose of neostigmine if it were intended subsequently to paralyse the patient with tubocurarine. Our experimental design was therefore limited and we were surprised to find that pretreatment with low doses of neostigmine did not fail to prevent the immediate onset of neuromuscular block in the isolated arm 5 min later. As the block occurred within 30 s of inflating the tourniquet, it is unlikely to have been influenced by "anoxic changes".

S. A. FELDMAN
London

PHARMACOKINETICS

Sir,—Professor Norman's timely and lucid editorial (1980) focused attention upon the limitation of pharmacokinetic modelling of muscle relaxant drugs.

As Professor Norman reported I have likened this fashionable preoccupation to a "pop art" form (Feldman, 1980a) and have described it as a psuedo science (Feldman, 1979). To subject scientific fact to a personal (and occasionally idiosyncratic) interpretation in order to reproduce it at great expense in another graphic form does for the plasma decay curve of a drug what Mr Warhol did for cans of soup. Just as Mr Warhol's paintings do not make the original more readily understood, so analog modelling does not increase the usefulness of the original data; indeed, because artistic licence is used to conceal lack of fundamental knowledge, it is likely to reach conclusions less valid than the original (Feldman, 1980b).

The plasma decay curve of a drug is the mean of many simultaneously occurring processes—distribution to various organs, each with its own rate process and affinity; of excretion and in some cases metabolism. These events can be affected by the mode of drug administration, previous medication, cardiac output, regional blood flow, hydration and by pathological and physical processes. To lump them all together and to treat the mean in a mathematically rigid format is simplistic, however complex the actual formula may be.

Professor Norman also raises the vexed question of where to put the receptors. In two-compartment models they are placed in the second slow phase, whereas in the more sophisticated three-compartment models they lie in a separate equilibrium volume (Hull et al., 1978). Evidence that equilibrium between plasma and receptors can occur during the second phase is lacking, indeed it is quite possible to have a differing degree of neuromuscular block in the two arms of the same patient. Since the onset of receptor occupancy can be demonstrated to occur within 40 s of drug administration if muscle blood flow is high (Feldman, 1976), it suggests that the receptors lie in the primary distribution volume. This is supported by finding that pathological processes such as liver disease, which increase this compartment size, necessitate more drug to produce the same degree of block and has been confirmed in a series of recently completed experiments by Dr Findley and myself in which we have contrived a method of "bio-assay" at times ranging from 60 s to 7 min following the injection of a bolus of drug. By this means it can be clearly demonstrated that, even after 90 s, the blood concentration of drug had decreased sufficiently to produce substantially less block, a process which is virtually completed in 5 min, that is within the time-course of the first compartment.

As Professor Norman states, the receptors were placed in the second compartment because parallelism can be demonstrated between the twitch height and plasma concentration during recovery from neuromuscular block (Matteo, Spector and Horrowitz, 1974; Shanks, Somogyi and Triggs, 1979; Sheiner et al., 1979). However, to demonstrate a casual relationship does not establish a causal principle (Huff, 1973). It ignores evidence that it is possible to have the same degree of recovery from neuromuscular block (50%) with a three-fold difference in plasma concentration (Agoston, Feldman and Miller, 1979) and that in certain pathological states it is possible to have a plasma concentration five times that of controls at the same degree of block (Martyn et al., 1980). Any relationship between plasma concentration and twitch response indicates the extent to which the receptor–plasma concentration gradient affects removal of drug from the neuromuscular synapse following dissociation from the receptor.

I would take issue with Professor Norman on only one point and that is the utility of exercise. I believe that even with the best model, to administer drugs on a predetermined computer-directed schedule would be to invite the sort of disaster that occurred with thiopentone at Pearl Harbour. It is far better to enrich our hospital fare with the produce of the real tins of soup rather than the pop art form, and to treat our patients in accordance with the findings of true research rather than the computer-processed reproductions of the analog model.

S. A. FELDMAN
London

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Sir,—The purpose of my leader was to examine the value of pharmacokinetic analysis in determining how much effect an injection of a drug would have and for how long. Some broad generalizations are now possible for the neuromuscular blocking drugs: renal failure will prolong the action, as may obstructive jaundice. With cirrhosis it may be that larger initial doses are needed, although the duration of action is prolonged, but the studies often show only what we can expect on the average. In addition there is wide individual variation. With neuromuscular blocking drugs the answer to the anaesthetist's question is to use a nerve stimulator: individual variation will be demonstrated.

Dr Feldman has demonstrated that other individual circumstances such as manner of testing, the technique of administration and the alteration of the local environment of muscle will alter the response to neuromuscular blockers. From this evidence he deduces the pharmacokinetic approach to be invalid. It is—in his circumstances, but not for most of us who do not apply such rigid tests.

Perhaps the use of one-, two- or three-compartment modelling is justified if we use Ockham's razor. Cohen, Corbascio and Fleischli (1965) carried out an early study on the distribution and fate of tubocurarine. As a result of analysing several tissues they were able to propose a nine-compartment analog model. Yet the decay in plasma concentration in their experiments can be described using two exponential processes (Smith, 1976).

Dr Feldman compares pharmacokinetic and pharmacodynamic modelling with Andy Warhol's pictures. These may not be exact representations, but they are illuminating. So may be these sciences.

JOHN NORMAN
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ADH CONCENTRATIONS AND PREMEDICATION

Sir,—We have been interested in the endocrine and metabolic stress response initiated by anaesthesia and especially by surgical trauma (Kehlet, 1979). Antidiuretic hormone (ADH) is regarded as one of the stress indicators (Felst et al., 1978). We studied the effect of premedication on ADH concentrations in 37 healthy patients undergoing major gynaecological operations under general anaesthesia. Thirteen patients received tofizopam 100 mg orally on the night before operation, and 100 mg on the morning of operation; 12 patients received nitrazepam 5 mg and 12 patients received placebo. ADH concentrations were measured by direct radioimmunoassay according to Fyhrquist, Wallenius and Hollemans (1976), modified with sequential saturation. The subjective assessments of premedication were recorded in the operating room just before the induction of anaesthesia (apprehension and excitement: nil, slight, moderate, marked). In this respect there was no significant difference between the patient groups, nor was any significant change recorded in the ADH concentrations: tofizopam group = $6.2 \pm 0.7\,\mathrm{pg\,ml^{-1}}$ before premedication and $6.4 \pm 0.7\,\mathrm{pg\,ml^{-1}}$ before induction; nitrazepam group = $5.6 \pm 1.2\,\mathrm{pg\,ml^{-1}}$ and $5.8 \pm 1.2\,\mathrm{pg\,ml^{-1}}$; placebo group = $5.1 \pm 0.8\,\mathrm{pg\,ml^{-1}}$ and $6.2 \pm 1.4\,\mathrm{pg\,ml^{-1}}$ (mean ± SEM). However, in each patient group, some ADH concentrations increased (from $4.9 \pm 0.6\,\mathrm{pg\,ml^{-1}}$ to $7.5 \pm 1.0\,\mathrm{pg\,ml^{-1}}$, $P < 0.01$, Student's t test, paired data, $n = 18$), and in others they decreased (from $6.2 \pm 0.8\,\mathrm{pg\,ml^{-1}}$ to $4.9 \pm 0.8\,\mathrm{pg\,ml^{-1}}$, $P < 0.001$, $n = 19$). The patients in the former group felt more excitement ($\chi^2 = 4.350$, $P < 0.05$) than those in the latter group and when the results of excitement and apprehension (equivalent to anxiolytic effect) were combined, the difference was even more significant ($\chi^2 = 6.195$, $P < 0.025$). Thus it appears that the endocrine stress response can be initiated before the induction of anaesthesia.

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JET VENTILATION FOR LARYNGEAL MICROSURGERY

Sir,—Steward and Fearon (1981) state that "the use of jet ventilation via a cannula into the trachea appears to be a very dangerous practice" and in their opinion should be abandoned. It is their recommendation that insufflation with spontaneous ventilation is the preferred technique. This technique may suffice for laryngoscopy, but it is unacceptable for carbon dioxide laser microlaryngeal surgery. The surgical application of the carbon dioxide laser requires a motionless "target". During spontaneous ventilation, the vocal cords are in motion, seriously interfering with the surgical technique.

We have performed more than 450 microsurgical procedures of the larynx utilizing the carbon dioxide laser. Our anaesthetic technique involves complete neuromuscular paralysis, i.v. anaesthesia and jet ventilation with oxygen via a 14-gauge needle placed in one of the four channels of the Abramson–Dedo laryngoscope. The tip of the ventilating needle lies just beyond the opening of the vocal cords (Ruder et al., 1981). Early in the development of this technique, pneumothorax occurred on two occasions (Oliverio et al., 1979). We have eliminated this complication by initiating ventilation with low inflation pressures (33 kPa in children and 100–130 kPa in adults).

It was also mentioned that "seeding of papillomata into the trachea" would seem to be increased if jet ventilation were applied (Fearon and MacRae, 1976; Steward and Fearon, 1981). About 40% of our patients were children with papillomata and we have no evidence of any tracheobronchial spread of this disease.

Since the laser vaporizes tissue and there is virtually no bleeding, we maintain that this technique is superior to the alternative methods utilizing aluminum foil-wrapped or metallic endotracheal tubes (Oliverio and Fermon, 1979) during carbon dioxide laser surgery of the larynx. These tubes must be inserted through the papillomatous area into the trachea before any laser treatment.

In our technique the use of the jet ventilating needle eliminates the danger of inadvertently cutting an endotracheal tube with the hi-energy laser beam (Ruder et al., 1981), it provides a completely open surgical field and it allows adequate ventilation in the paralysed patient. The availability of four channels in our laryngoscope, allows the surgeon the freedom to place the ventilating needle away from the lesion and pointed directly down the trachea, thereby avoiding any trauma to the tracheal mucosa.

Another advantage of the jet ventilation technique over general anaesthesia by insufflation is that the latter provides no method for scavenging anaesthetic gases; the jet injector utilizes oxygen only.

We believe that the jet ventilation technique is the method of choice for carbon dioxide laser microsurgery of the larynx, and is preferable to insufflation with spontaneous ventilation.

R. M. Oliverio, jr
C. B. Ruder
A. L. Abramson
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RESUSCITATION OF THE NEONATE

Sir,—As I read the recent article on this topic (Rosen et al., 1981) I began to feel a quiet delight that at last the phenomenon of the "staircase pattern" of expansion of the neonatal lung—a process which was fairly generally known even 20 years ago—and its implications respecting schemes of resuscitation, was being acknowledged by a few more clinicians. My expectations were dashed when further reading revealed that the Cardiff workers were intent upon describing yet another piece of apparatus.

As Rosen and his colleagues suggest, clinical judgement is the key to successful, non-injurious resuscitation. I fail to follow the logic which impels them to advocate an apparatus which requires the resuscitator not only to alter the blow-off pressure periodically, but also to time, in seconds, the intervals between such alterations. At the same time he is required to monitor the heart rate and other clinical attributes of the neonate. That is surely making too great a demand of the abilities of most of our (junior) clinicians who are called upon to resuscitate infants.

At the risk of causing tedium, may I reiterate my view that the only sensible, and least harmful, method of resuscitation, when the trachea is intubated, is that of intermittently puffing oxygen through the tube, using the cheeks as bellows. This ensures that a constant watch is kept, at eye level, on the anterior chest wall, providing evidence of expansion of the lungs and, by the exercise of "clinical judgement" of a fairly low order, guarding against excessive expansion. The "educated cheek" is no more difficult to acquire than is the "educated hand". Furthermore, one hand of the resuscitator is left free so that, by lightly grasping the base of the umbilical cord between finger and thumb, the approximate heart rate and its response to resuscitation may be continuously monitored. Simple, effective, with no distracting apparatus and no valves which could stick or become clogged.

J. Selwyn Crawford
Birmingham

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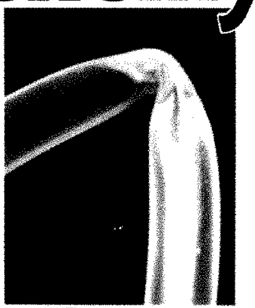

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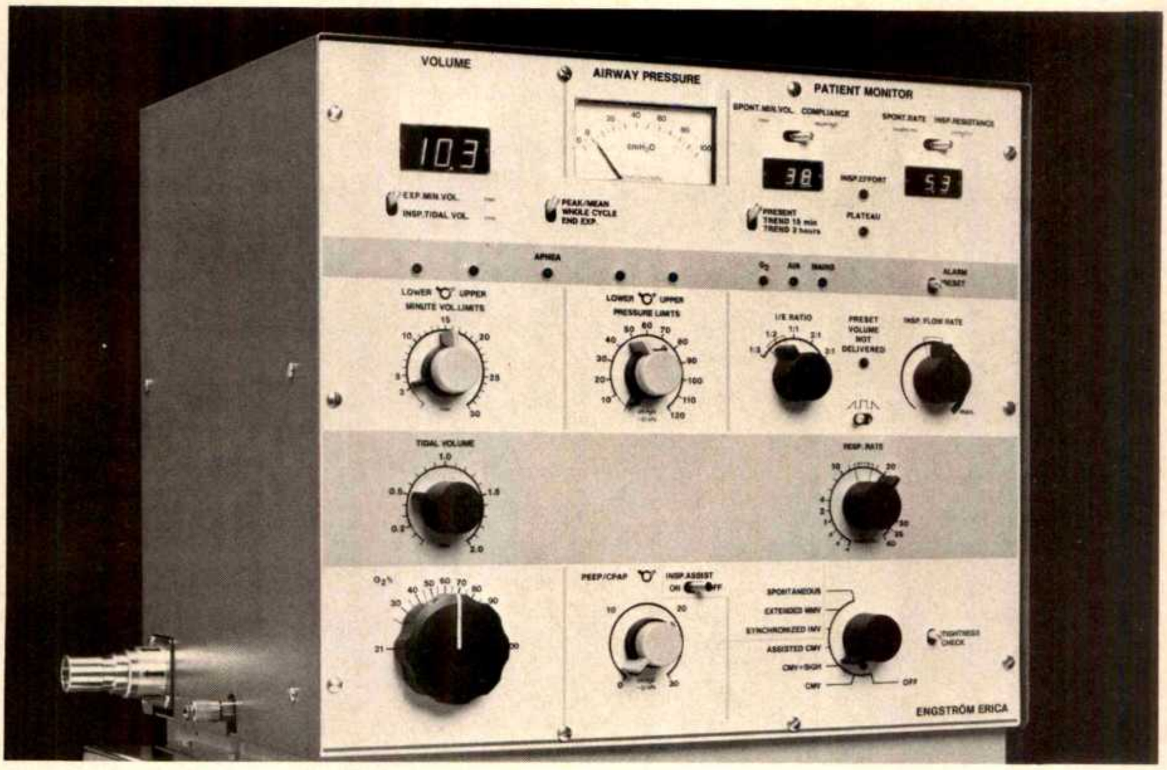

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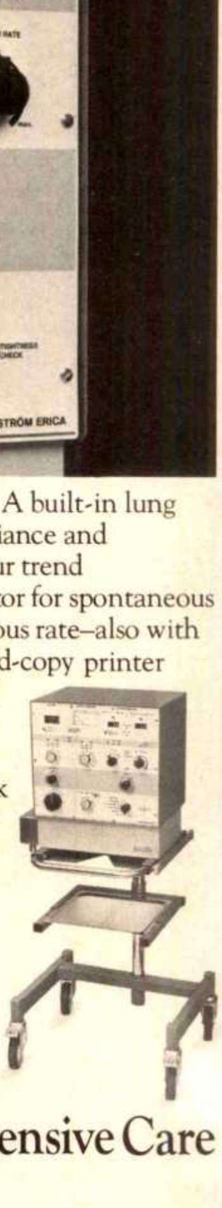

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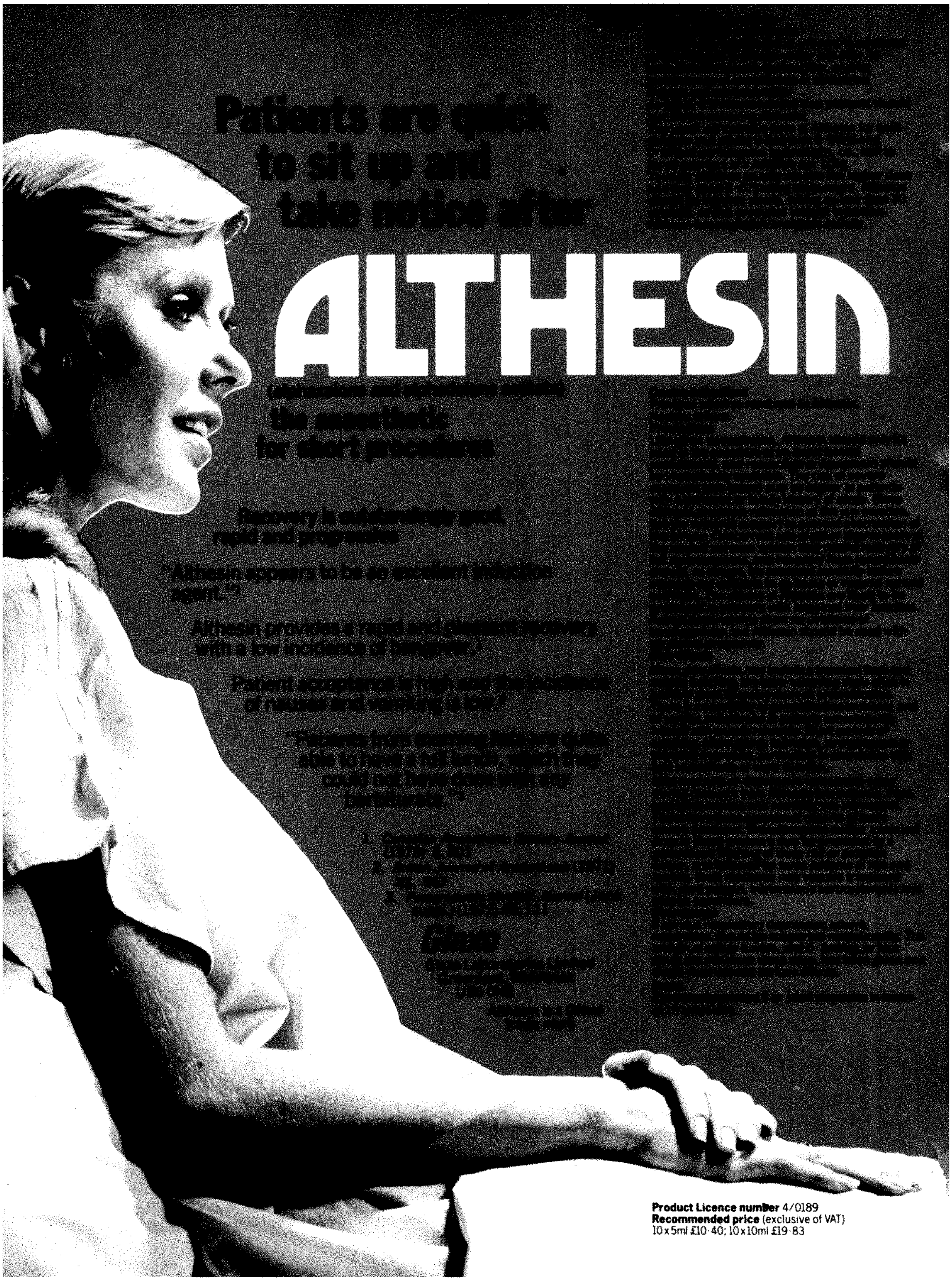

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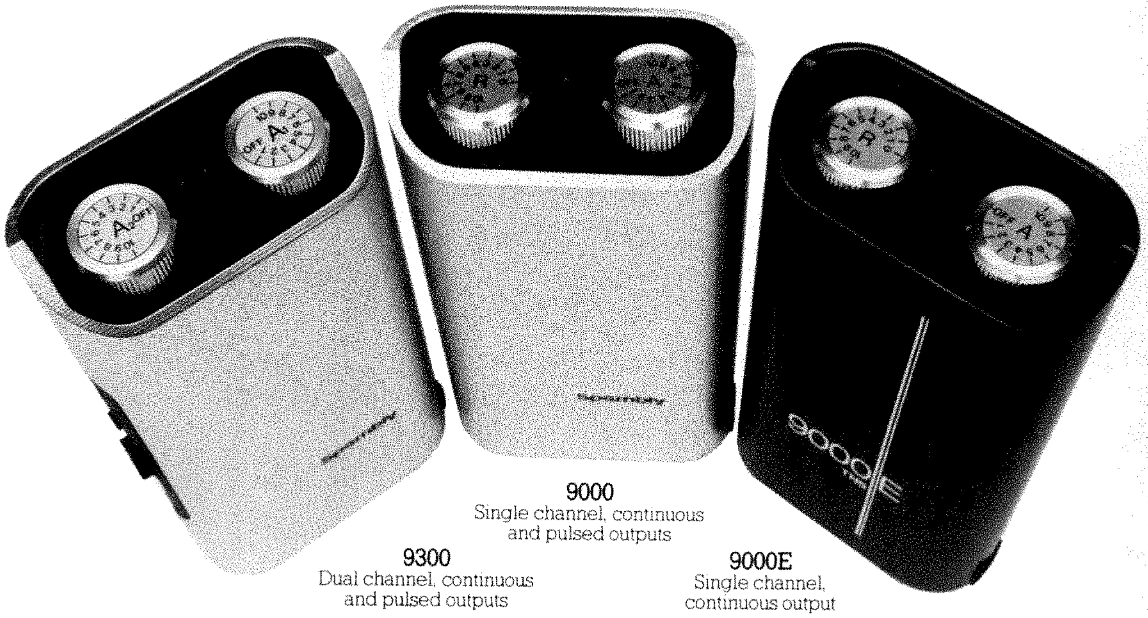

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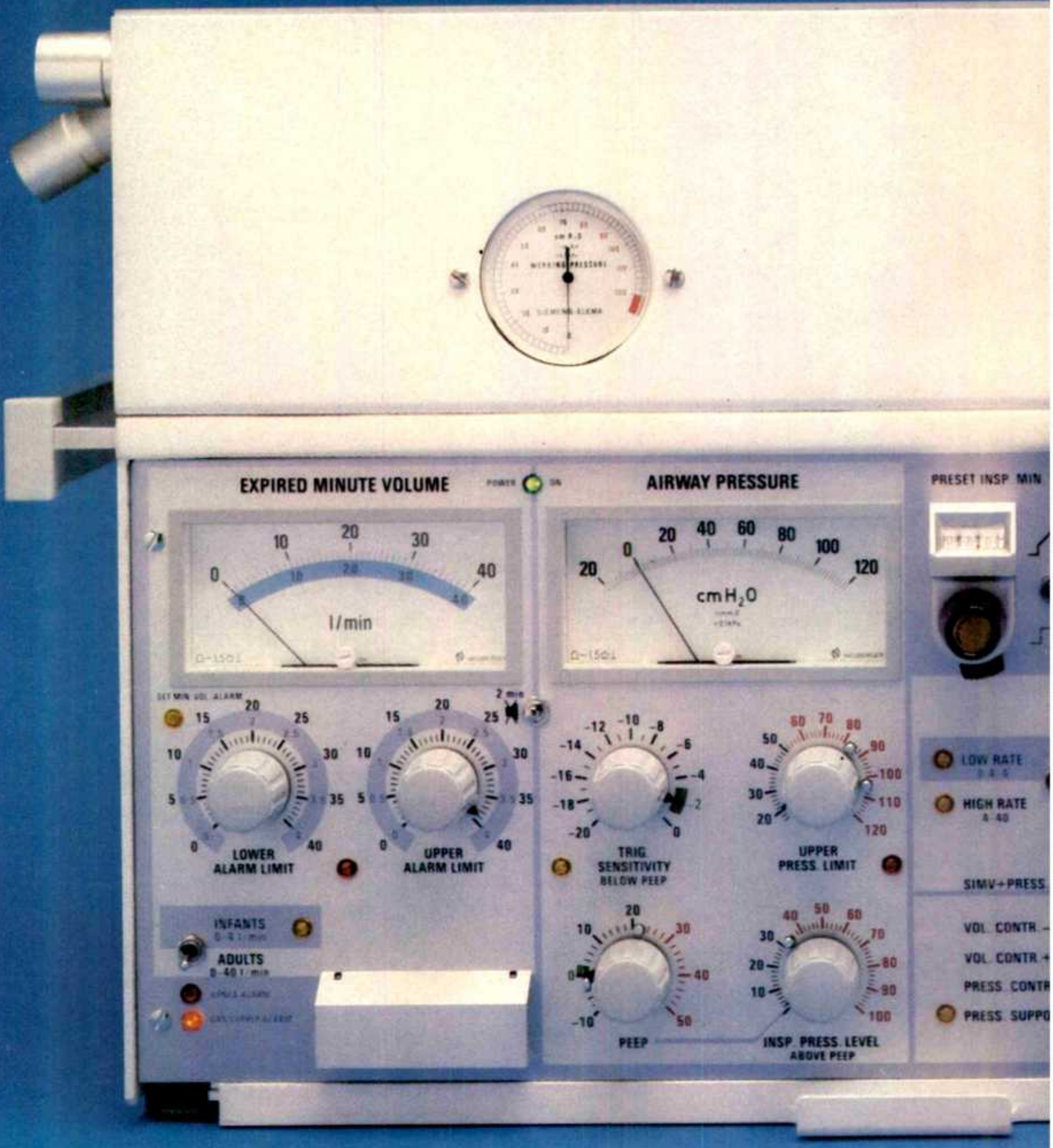
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- Introduction (not headed)
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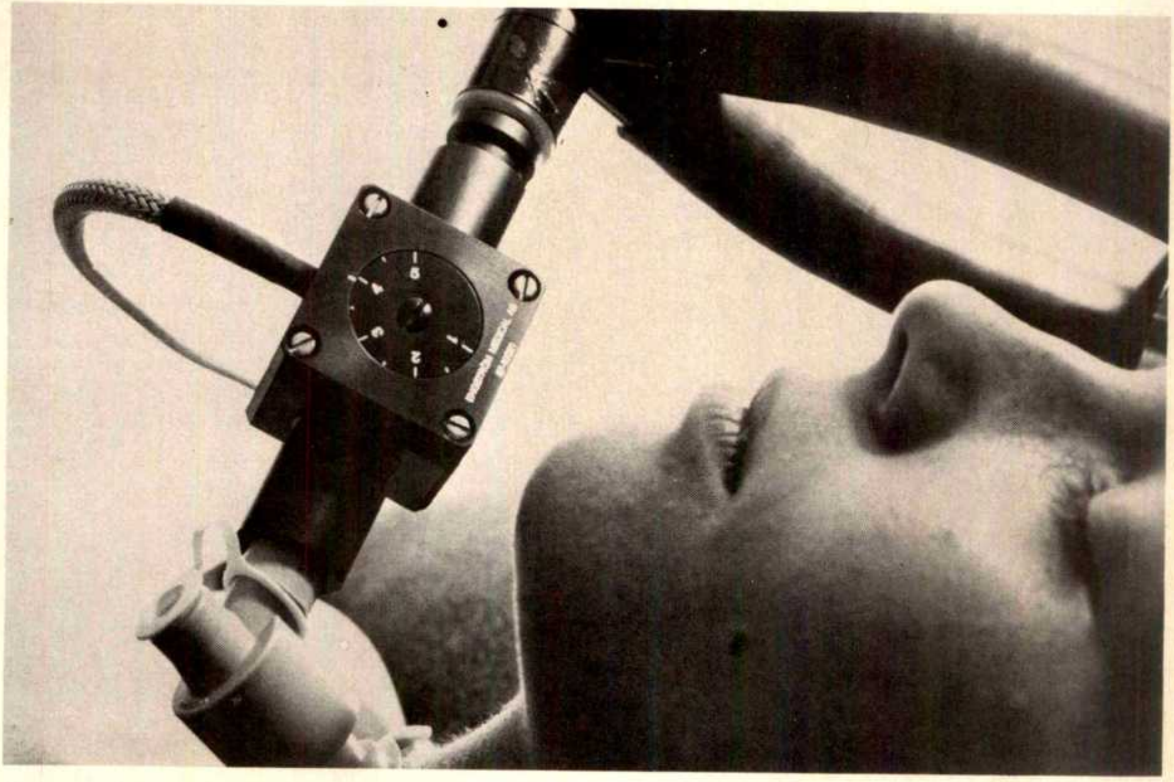

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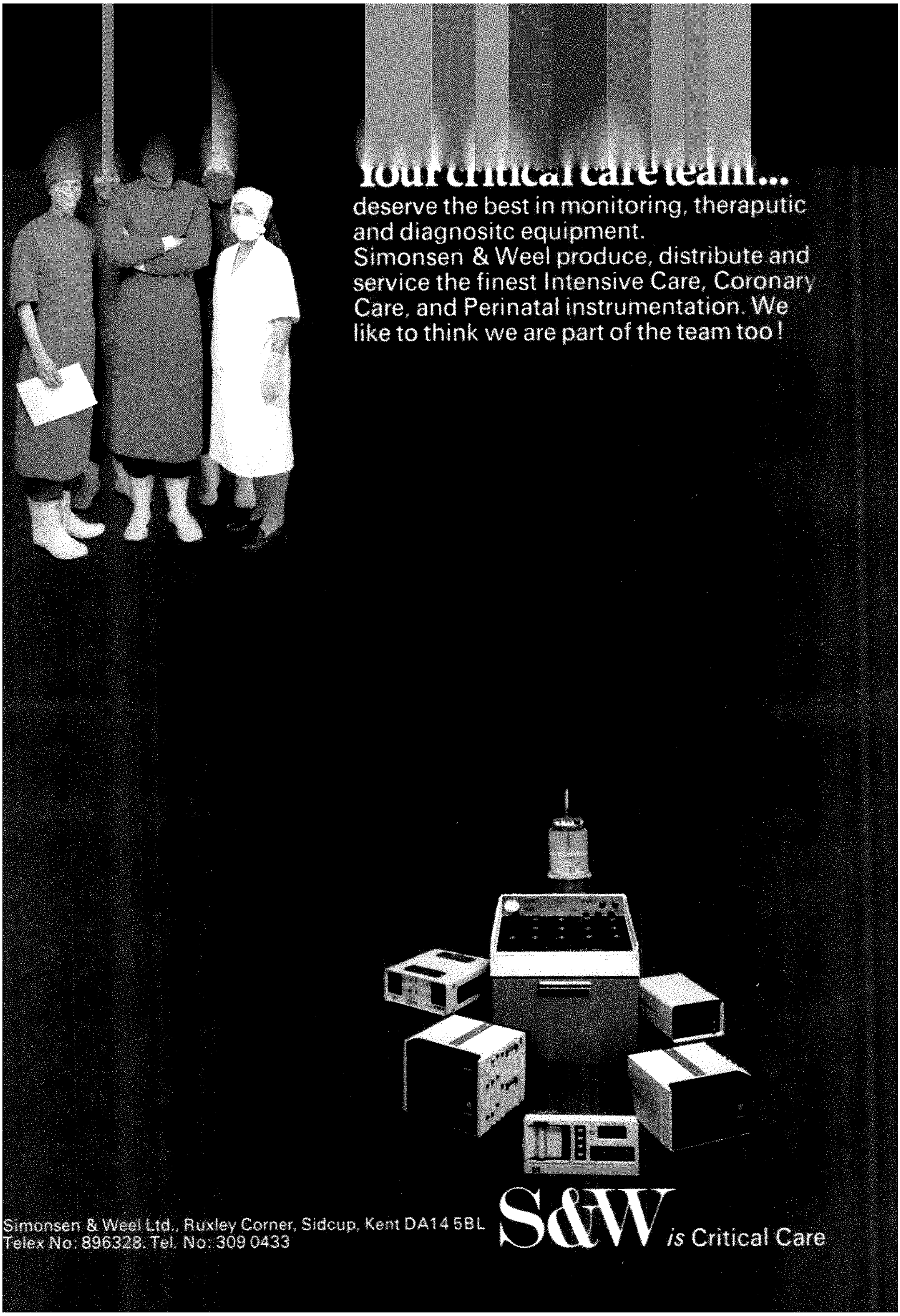

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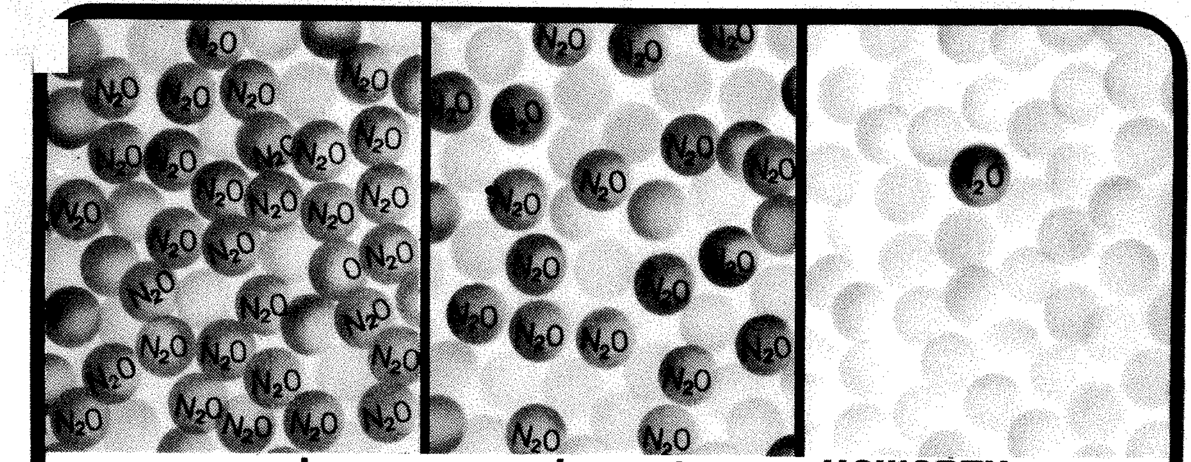

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EDITORIAL

BRAIN DEATH

B. JENNETT

Death is a process rather than an event. The point in this process when death can safely be declared is a matter for society to decide, taking account of the natural concern that this should never be done too soon. In the eighteenth century fear of premature burial led to all kinds of ingenious devices to enable victims of such a mistaken diagnosis to signal to the living that they too were alive. In 1740 a paper entitled "The Uncertainty of the Signs of Death and the Danger of Precipitate Internments" concluded that putrefaction was the only sure sign of death. A century later these fears were largely allayed by the intervention of the stethoscope, which focused attention on the heart beat as the ultimate sign of life. The mid-twentieth century saw the matter complicated by another invention—the portable lung ventilator. When used to treat temporary respiratory failure this can save lives; but when breathing stops because of irreversible brain stem damage, mechanical ventilation serves only to prolong the process of dying, as different organs in turn cease to function. In 1968 the WMA Declaration of Sydney stated that the point of death of different organs and cells is not so important in determining the death of the individual as is the certainty that the process has become irreversible. In the ventilated, brain-damaged patient the heart can beat for days after the brain has not only ceased to function but has begun to decompose. To continue ventilation in these circumstances is to deprive the patient of death with dignity, and needlessly to prolong the distress of the family; it is also an inappropriate use of staff and facilities. To avoid these undesirable consequences of protracted attempts at resuscitation doctors need to consider how to recognize when the brain is dead, so that ventilation can be discontinued.

THREE MISCONCEPTIONS

Public concern about brain death in Britain was precipitated in October 1980 when the BBC broadcast to 6 million viewers a *Panorama* programme entitled 'Transplants—Are the Donors Really Dead? Three quite different misconceptions figured prominently in that programme, and they provided the focus for the spate of comment and correspondence that followed in both the public and the medical press.

History of brain death

Panorama hinted that the concept of brain death was something new, that had been introduced without ever having been properly discussed. In fact doctors have been dealing with brain death for about a quarter of a century. The Korean campaign of 1950–53 saw the first widespread use of lung ventilators for the victims of trauma; the poliomyelitis epidemics in 1952 in Denmark and in 1955 in New England saw further applications of ventilators. Intensive care units were established in 1958 in Oxford, Baltimore and Toronto (Pontoppidan et al., 1977), the same year that the value of respiratory intensive care for severe head injuries was reported from Newcastle-on-Tyne (McIver, Frew and Matheson, 1958). The next

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year saw the first formal description of brain death by two Parisian neurologists (Mollaret and Goulon, 1959), who termed it "coma dépassé". Ten years later the Harvard criteria for the diagnosis of brain death were published by a committee that included lawyers and theologians as well as neurologists and neurosurgeons, under the chairmanship of Henry Beecher, Professor of Anaesthesia (Report of the Ad Hoc Committee of Harvard Medical School, 1968). Several discussions of brain death appeared in British journals (Editorial, 1974; British Transplantation Society, 1975; Editorial, 1975; Jennett, 1975) before the Conference of Medical Royal Colleges and their Faculties of the U.K. (1976 a,b) published, in both the *British Medical Journal* and the *Lancet*, a statement on the diagnosis of brain death. These "U.K. Criteria", as they came to be known, resulted from 2 years of discussion between anaesthetists, neurologists, neurophysiologists and neurosurgeons. Only when a further year had passed with no word of adverse comment did the Chief Medical Officers of the Health Departments send copies to all hospital doctors. The U.K. criteria were subsequently reprinted in the Health Departments' (1979) Code of Practice that resulted from a working party which included doctors and nurses, and representatives of the legal profession and health councils, and which also sought the views of major religious bodies. There is therefore no substance in the charge that the concept of brain death was introduced in Britain without adequate opportunity for discussion.

Relation to organ transplantation

Panorama's second innuendo was that the diagnosis of brain death had emerged largely because of the need to find organs fit for transplantation. In fact these two technological phenomena developed quite separately, although both did so in the mid-1950's; however, brain death became commonplace long before transplantation. It was not until 10 years after brain death was described that there was more than one transplant a week in the entire U.K.; in the early years many organs came from live donors—more than half in an American survey in 1971 (Moore, 1972). Cadaver organs are now the rule and by 1977 two-thirds of these came from brain-dead donors (on ventilators) in one British region (Barnes, 1979); more recently the same region reported that all its donors were now ventilated artificially (Barnes, 1981). What brain death has done for organ donation has been to remove the sense of hurry and unseemly haste, thereby making relatives more likely to agree to donation and to feel satisfied afterwards about what happened. But if an alternative to organ transplantation were discovered tomorrow there would still be thousands of brain-dead patients every year for whom a decision would have to be made about when to turn off the ventilator.

Reliability of the Criteria

Undoubtedly the most serious implication of the *Panorama* programme was that the criteria by which brain death is diagnosed in Britain might not be as reliable as those used in other countries, because too much attention was focused on the death of the brain stem and because diagnosis depended on clinical assessment. Several American doctors on the programme alleged that patients not infrequently recovered after a clinical diagnosis of brain death, and patients who had supposedly done so were interviewed. The next few months saw the publication of a considerable body of evidence, from both sides of the Atlantic, that supported the validity of clinical criteria for diagnosis; it also became obvious that not one of the American cases shown on *Panorama* would have been diagnosed brain dead by British criteria. However, it became clear that doctors did not all share exactly the same concept of the pathophysiology of brain death; this explains most differences of opinion about the relative importance of various diagnostic criteria. These differences appear to mirror successive stages in the evolution of thinking about brain death, as experience has accumulated in the past 25 years. Since the U.K. criteria were published relatively late in this evolution they reflect a more recent approach than do pronouncements of the early 1970's, which were based on the original Harvard document of 1968.

CHANGING CONCEPTS

The Harvard criteria required absence of all reflex motor activity, and a flat e.e.g. was recommended. This implied that the whole central nervous system was dead—cortex, spinal cord and brain stem. It has now become evident that it is the death of the brain stem that is crucial; once this part of the nervous system is dead then the heart always stops within days, even though ventilatory and other support is maintained. This empirical finding, now formally recorded in hundreds of published cases and found to be consistent in thousands more cases observed by numerous doctors in many countries, indicates that brain stem death is a sign that the process of death has passed the point of irreversibility on which the Declaration of Sydney put so much emphasis.

What also emerged, as experience accumulated, was that co-ordinated reflex activity in the spinal cord could persist for days after brain death; indeed, reflex movements of the limbs tend to reappear, or to become more active, if ventilation is maintained for long after the brain stem reflexes have all disappeared. More recent criteria therefore make a point of noting that spinal reflex activity is compatible with brain death.

The question of residual activity persisting in parts of the cerebral cortex for some time after the brain stem is dead has given rise to more debate. Physiological evidence indicates that integrated cortical function is possible only if there is upward driving from the brain stem via the ascending reticular formation, when this is interrupted under experimental conditions both the electrical and the metabolic activity of the cerebral cortex is greatly depressed. Moreover, when the cerebral cortex undergoes massive hypoxic necrosis after cardiac arrest the clinical condition that results is the same as when the intact cortex is disconnected by widespread axonal tearing associated with head injury—namely the vegetative state (see below). What is certain is that physico-chemical activity can continue for some time in isolated areas of cortex above a dead brain stem, as indeed it can in brain slices on the laboratory bench. Residual electrical activity is not infrequently recorded on the e.e.g. after the brain stem is dead, but this has been shown to make no difference to the outcome (Pallis, 1981).

For these reasons the concept of brain death now focuses on the brain stem. If the brain stem is dead, the brain is dead; and if the brain is dead, the person is dead. The time of death is when brain death is diagnosed, not some later time when the heart stops (Conference of Medical Royal Colleges and their Faculties of the U.K., 1979). The acceptance of these concepts by society is manifested in many places by the enactment of brain death laws—the first American state to do so being Kansas in 1970, and the first European country Finland in 1971. The essence of such laws is to make it clear that once a person has been declared brain dead by accepted medical standards then he can be regarded as legally dead; but such laws (with few exceptions) make no attempt to specify the technical criteria by which brain death is to be diagnosed. The value of such laws is that they dispose of any ambiguity about the action of a doctor who discontinues artificial ventilation after making the diagnosis of brain death. He is not withdrawing treatment in order to let a person die; he is simply stopping doing something useless to someone who is already dead.

CRITERIA FOR DIAGNOSIS

Given these concepts it follows that what is required of criteria is to demonstrate beyond doubt that the brain stem has irreversibly ceased to function. That was certainly the objective of the criteria published by the U.K. Royal Colleges, and subsequently endorsed by the Departments of Health. These criteria have two components—the pre-conditions and the tests. Only when the pre-conditions have been satisfied is it appropriate to proceed with the tests.

The *pre-conditions* require that the patient is in deep coma and that he is apnoeic (that is receiving artificial ventilation), that there is irremediable structural damage of the brain, and that reversible causes of brain stem depression have been excluded. The last includes physiological depressants such as hypothermia and gross metabolic imbalance, as well as depressant drugs (including alcohol), or neuromuscular blockers used to facilitate endotracheal intubation or to maintain mechanical ventilation before there was apnoea. When relaxant drugs have been given a peripheral nerve stimulator can be used to show whether these are still causing paralysis.

In most cases the diagnosis of irremediable structural brain damage is obvious, and there is no serious concern about confusing factors. More than half the cases of brain death that occur in Britain are the result of overwhelming head injury; the story is clear and there is no reason to believe that antecedent factors are affecting brain function—other than recent alcohol intake in a proportion of patients. Spontaneous intracranial haemorrhage accounts for almost another one-third of the cases; their story is of becoming unconscious after sudden headache and evidence includes stiff neck, subhyaloid haemorrhages and bloody c.s.f. Most of the remaining cases are patients who have not responded to treatment for other intracranial conditions, such as brain tumour or abscess, perhaps encephalitis or meningitis; and there are a few patients who have failed to respond to resuscitation after an episode of cardiac arrest or profound hypotension which has caused hypoxic brain damage.

Sometimes the story is less clear-cut, for example when a patient became apnoeic just before, or very soon after admission to hospital, and the preceding events are not fully known. Or a patient may have been found unconscious with no witnesses to say what happened; in spite of an obvious head injury it is sometimes uncertain exactly what the patient was like just before being injured. In such instances it is necessary to consider the effect of drugs that may have been taken or administered; if these cannot be measured, the doctors must wait long enough to allow exclusion of drugs as the cause of brain stem depression.

The *tests* that are applied, once the pre-conditions have been met, are to determine if there is any evidence at all of residual or returning activity in the brain stem. Various reflex responses are tested—of the pupils to light, of the eyelids to corneal touching, of the muscles of the throat to movement of the endotracheal tube, of the facial muscles to pain applied to the face and forehead. Then the ears are syringed with 20 ml of ice-cold water (checking first that the meatus is clear down to the drum), and the eyes watched for movement. If there is any response to any of these, then the brain stem is still functioning.

The final and most crucial test is to confirm that there is no return of respiratory drive from the brain stem. An American neurologist has commented on the importance of this test—and that precise specifications about how to carry this out are a feature of the U.K. criteria (Homan, 1979). The patient is disconnected from the ventilator for long enough to allow Pa_{CO_2} to increase to a threshold value whilst maintaining diffusion oxygenation to avoid hypoxaemia. The Pa_{CO_2} of the brain-dead patient receiving artificial ventilation may be quite low, and the rate of increase of carbon dioxide in such a metabolically depressed subject is also less than normal. The threshold for stimulating breathing in patients suspected of brain death has been reported to be 45–56 mm Hg, which is considerably greater than for the anaesthetized patient with a normal brain (Schafer and Caronna, 1978). How long a period of disconnection is required depends on the starting value of Pa_{CO_2}, which may be brought up to normal by administering 5% carbon dioxide in oxygen before disconnection. According to Schafer and Caronna (1978) a period of 10 min disconnection is long enough to ensure Pa_{CO_2} 60 mm Hg, provided the starting value is greater than 30 mm Hg. Special consideration is needed in subjects with chronic respiratory insufficiency who are accustomed to a high resting Pa_{CO_2}.

CAUSES, CIRCUMSTANCES AND FREQUENCY OF BRAIN DEATH

Head injury is the commonest cause of brain death in Britain, accounting for about half the cases. Respiratory failure may occur soon after the patient reaches hospital; alcohol, and hypotension or hypoxia from associated injuries, may be complicating factors. Respiratory failure may occur in patients who have been recovering from the impact injury but have developed secondary complications such as intracranial haematoma or brain swelling. Similarly, with intracranial haemorrhage there may be respiratory failure soon after the initial ictus; or it may be a secondary event following rupture of an aneurysm a second time after recovery from the initial bleed. Temporary apnoea is common immediately after subarachnoid haemorrhage and may recover spontaneously in a minute or so, but in a few patients recovery occurs after 1 h or more of apnoea, if artificial ventilation has been maintained during this period. This possibility makes it justifiable to institute ventilation in such cases, although a frequent result is that the patient becomes brain dead.

Brain death may also occur when treatment for other intracranial conditions (such as abscess, tumour, encephalitis or meningitis) proves fruitless. Such patients will usually receive artificial ventilation as part of the treatment and it gradually becomes obvious that they are brain dead. Sometimes patients with recurrence of an intracranial tumour that is known to be inoperable, and in whom the decision has already been made that no further treatment is appropriate, may receive artificial ventilation during terminal apnoea because their family have previously agreed to this in order to make organ donation possible. They are therefore in a different category from the majority of brain-dead patients, in whom resuscitation or active treatment has failed.

Another group of patients are those who have suffered cardiac arrest or profound systemic hypotension and in whom heart action and circulation have been restored, but too late to save the brain. According to the duration and intensity of the hypoxia these patients may be brain dead, or may be left in the vegetative state (see later). A few recover with lesser degrees of brain damage, and some recover completely. Such a hypoxic episode of brain damage may complicate head injury or some other cerebral condition, and it may then be difficult to apportion the relative contributions of the primary brain lesion and the secondary hypoxic damage. The importance of trying to do so is that recovery is possible after several hours of unresponsive coma when this is a result of purely hypoxic damage, perhaps because biochemical sequelae of tissue hypoxia can account for continued but reversible depression of brain stem activity.

There is no direct way to discover how frequently brain death occurs nationwide or its distribution between hospitals or specialties. Small series have been reported from two general intensive care units (Luksza, 1979; Searle and Collins, 1980), and three neurosurgical units recently combined their experience over several years in a review of more than 600 cases (Jennett, Gleave and Wilson, 1981). Patients dying from acute brain damage are ventilated terminally more often than was the case 5 years ago; about half of the fatal head injuries in neurosurgical units now go through a period of brain death before the heart stops. Calculations based on these studies, and on epidemiological data about head injuries and other conditions that frequently result in brain death, indicate that there are about 4000 cases annually in Britain. In countries where ventilator treatment for acute brain damage is more widely practised, brain death will probably be more frequent; also where fatal head injuries occur more often—the annual rate in many countries is more than twice that in Britain (Jennett and MacMillan, 1981; Jennett and Teasdale, 1981).

Records about organ donors from all over Britain are centrally collated by the U.K. Transplant Service, from which some deductions can be made about the distribution of brain death in different types of hospital. Although only one brain dead patient out of every four or five becomes a donor, even in units committed to securing organs (Wilson and Cast, 1980; Jennett, 1981), donors reflect closely the diagnostic distribution of the total pool of brain dead patients from which they are drawn. A review of more than 1200 donors during 1978–1980 showed that three-quarters of 285 hospitals which had at least one donor were neither teaching hospitals nor had a neurosurgical unit (Jennett and Hessett, 1981). Many of these district hospitals were relatively small and at a distance from regional neurosurgical units. Most general intensive care units have about 8–10 cases of brain death each year, whereas a large regional neurosurgical unit might have five times as many or even more; but there are so few of these that the majority of cases of brain death are in non-specialist units.

VALIDATION OF CRITERIA

Because the diagnosis of brain death now usually leads to withdrawal of artificial ventilation, with consequent cardiac arrest, it has been alleged that the diagnosis is a self-fulfilling prophesy. In fact it was many years before clinicians developed the confidence to act logically by discontinuing ventilation as soon as the diagnosis of brain death was made. It took 19 years in one British neurosurgical unit for the proportion of cases in which ventilation was discontinued to increase from 6% to 40%; even in 1980 about one-third of patients declared brain dead developed cardiac asystole whilst ventilation was being continued (Jennett, Gleave and Wilson, 1981). More than 700 patients have now been formally reported in whom ventilation was continued after the *clinical* diagnosis of brain death; in all cases the heart stopped within 14 days, usually much sooner (Editorial, 1981). To these published reports must be added the accumulated experience of clinicians in many countries. Since the publication of the Harvard criteria of 1968 it is estimated that at least one-quarter of a million cases of brain death have been observed. In this time there have been no adequately documented exceptions to the empirical observation that brain stem death is a reliable predictor of cardiac asystole, and that the process of death has reached the stage of irreversibility.

A different approach to validation is to analyse the early clinical features of patients who have survived a period of deep coma to find out whether, in their worst state, any might even have been suspected of being brain dead. This was done for a series of 1003 such patients who were alive 3 months after a severe head injury, and details of whose early clinical course had been prospectively recorded in a computerized data bank. Not one of these patients had ever had a combination of apnoea, fixed pupils, absent eye movements and other unresponsiveness ascribed to brain damage (Jennett, Gleave and Wilson, 1981).

ALLEGED NEAR-MISTAKES

In spite of the weight of evidence which supports the reliability of clinical criteria for diagnosing brain death, occasional newspaper stories have appeared, mostly in the early 1970's, of patients recovering after allegedly being considered brain-dead. In some of these instances it was further suggested that organs were "nearly" taken for transplantation. Once full details are discovered such incidents are readily explained by one or another of a variety of misunderstandings. Sometimes the basis of the rumour is no more than that a relative was told soon after the patient was admitted that the outlook was "almost hopeless". That is very different from a declaration of brain death by strict criteria; it should cause no surprise that some such patients respond to vigorous resuscitation—that is what resuscitation aims to achieve. In these circumstances a doctor would not raise the matter of possible organ donation, but relatives quite often do so now that awareness of the need for donors has increased. The doctor should explain that it is too soon to know whether it will come to that, whilst thanking the relatives for the offer. Sometimes doctors may unwisely pursue the matter of donation (or even initiate discussion of this possibility) before there has been time to satisfy the pre-conditions. Even if the acceptance of the offer of a donor has been explained as being conditional on the patient failing to respond to resuscitation, this is easily forgotten by distraught relatives.

Occasionally brain death has been suspected, at least for a time in somebody's mind, in patients suffering from unresponsive states other than brain death and readily distinguishable from it. The most common of these is the vegetative state, a condition that results from the cerebral cortex being out of action while the brain stem remains active (Jennett and Plum, 1972). The patient can therefore breathe and swallow (although often requiring tube feeding), but he has no psychologically meaningful responses to the environment. No words are uttered, but there are periods of wakefulness when the eyes are open, and they may follow moving objects reflexly. The spastic limbs have a considerable repertoire of reflex activity, including a grasp reflex that may be interpreted mistakenly as a voluntary movement. The commonest cause is severe head injury that isolates the cortex by severing the subcortical connections, but when hypoxic necrosis of the cortex follows cardiac arrest the clinical result is the same. Such patients can survive for years, given adequate nursing support. A much less common condition is the locked-in syndrome, which is a result of brain stem damage but in selective parts only. Such patients are paralysed below the face, because the down-going motor tracts are out of action—usually because of a vascular lesion. They are awake and can communicate by code, using blinking or movements of the eyes or jaws, which are spared because their nerve supply is above the lesion.

In all these instances brain death is suspected by someone in a patient who is in fact alive. Occasionally the opposite happens, in that a patient who is brain dead is believed by someone to be alive—because of the persistence of spinal reflexes. Anyone likely to witness these movements for the first time should be warned and have their nature explained, so that they will not misconstrue what they see. Other possible areas of misunderstanding have been reviewed above, and it is important to have these recorded and widely recognized—as was done before the U.K. criteria were drawn up (Jennett, 1975).

SAFEGUARDS

No adequately documented case of the erroneous diagnosis of brain death by the U.K. criteria has come to light, and the only British doctor claiming to know of such cases had to publish a retraction

(Paul, 1981). Even so it is important to consider what safeguards have been proposed and which are appropriate. The best safeguard is a well-written set of guidelines applied by medical and nursing staff who are familiar not only with the diagnosis of brain death, but also with how to deal confidently and sympathetically with the family. Most guidelines recommend that tests for brain stem function be repeated and that two doctors of adequate experience should be involved in making the diagnosis. When there is to be donation of organs, neither doctor should be associated with the medical team waiting to receive organs for transplantation. Apart from this there should be no difference in practice whether or not there is to be organ donation; the significance of the diagnosis of brain death is that it now normally leads to the discontinuation of ventilation which is then followed by cardiac asystole.

The medical skills required to diagnose brain death with confidence are not limited to the performance of the tests of brain stem function. Indeed, these tests are relatively simple, no qualitative interpretation of the responses being called for because the sign of brain death is that there is no response. Determining that the pre-conditions have been satisfied, on the other hand, calls for careful appraisal of the clinical setting—how reliable is the history of events before the occurrence of deep coma and apnoea—what is known about the cause of the brain damage—had enough time passed to be sure of the diagnosis? This is where the experience of the clinician counts.

An important safeguard against mistakenly suspecting brain death is to allow enough time to elapse. What matters is the interval between the onset of apnoea and the first tests of brain stem function. Sufficient time must pass to satisfy the pre-conditions, to allow the diagnosis to be established, to undertake such therapeutic endeavours as are needed to determine that the brain damage is irremediable; time, for example, to restore normotension and normoxia, to attempt to reduce intracanial pressure by surgical or non-surgical means, and for reversible factors to abate (for temporary apnoea to recover, or concentrations of drugs to decrease). How long this takes varies widely according to the circumstances. At least 6 h is needed for a patient becoming apnoeic soon after arrival at hospital with acute brain damage, and 12–24 h may often be required. Longer than may be necessary when the history is indefinite, when drugs are suspected, or when there has been an incident of hypoxia (either primary or secondary). Much less time is required for patients who develop secondary brain damage when already in hospital, and in whom the primary brain pathology has been discovered by investigation (for example, recurrent subarachnoid haemorrhage from a diagnosed aneurysm). The duration of artificial ventilation and of time in hospital for a series of patients with different conditions have been reported by Jennett and Hesset (1981). Codes of a decade ago emphasized the time interval between two sets of tests demonstrating brain death; it is now realized that, provided enough time has passed to satisfy the pre-conditions, these tests can be repeated after an interval of 30 min.

This section on safeguards might seem the obvious place to discuss those laboratory investigations that have been recommended by some as providing useful confirmatory evidence that brain death has occurred. The value and reliability of these, and their necessity for the diagnosis of brain death, is perhaps now the only important area of disagreement between doctors in different countries. Two types of test are most often proposed—those that measure blood flow to the brain and those that monitor the electrical activity of the cerebral cortex. Blood flow may be visualized by angiography or its presence deduced from the entry into and clearance from the head, of radioactive isotopes injected into the blood stream. Certainly, if absence of blood flow to the brain for 15 min can be shown it is conclusive evidence that the brain is dead; but some intracranial circulation can continue for a time after brain death. Moreover, the equipment and expertise required is not always available, whilst angiography carries some risk; even in the U.S. these are regarded as impractical tests for general use.

The e.e.g. is different, in that it is widely available in many countries and is certainly quite harmless. However, there are several reasons why it is unwise to regard it as an appropriate confirmatory test. The most important is that it is irrelevant, in that it assesses function in the cortex whilst brain death depends on loss of function in the brain stem. As already explained, some residual e.e.g. activity may persist for a while after brain stem death, but this does not alter the inevitability that cardiac asystole will soon occur (Pallis, 1981). Even when scalp electrodes show cortical silence, activity might be found in the thalamus by using depth electrodes—but no one seriously suggests making a burr hole for this purpose. In any event, electrocerebral silence on scalp recording is an arbitrary phenomenon, depending on agreed settings on the machine, on the technical expertise of the recordist and on the interpretation of the record. In the electronically hostile environment of the intensive care unit reliable recordings may be difficult to obtain. It is therefore misleading to imply that the e.e.g. provides an objective measure of brain death that is likely to be more reliable than clinical assessment. The most telling argument against its use, however, is that even if a technically satisfactory record is obtained, and is deemed to be flat by agreed standards, this does not necessarily indicate brain death. There are many reports of patients recovering from deep coma, after receiving depressant drugs or following cardiac arrest, whose e.e.g. was at one stage flat (Pallis, 1981). Thus the e.e.g. fails to distinguish between brain death and the condition that most closely mimics it.

Although an iso-electric e.e.g. figured prominently in the original Harvard criteria it was clearly stated the following year that it was not necessary for the diagnosis (Beecher, 1969; Sillito, 1969). Neurosurgeons in Minnesota emphasized this in 1971 (Mohandas and Chou, 1971) and have recently re-stated the case for making the diagnosis on clinical evidence only (Chou, 1981). Those who still maintain that it should be used are mainly specialists in clinical neurophysiology, and it is important to note that their severest critics are others of the same discipline (Legg and Prior, 1980; Pallis and MacGillivray, 1980, 1981; Prior, 1980). The U.K. brain death criteria expicitly state that e.e.g. is not needed for the diagnosis, and there is evidence that e.e.g. is being used less and less in many countries, including the U.S.A.

CONCLUSION

The attention focused on this topic during the past year in Britain has led to better understanding of the concepts and practicalities associated with brain death. It is now accepted as a relatively frequent event in most acute hospitals, where good medical practice demands that doctors learn to recognize it reliably, and compassion requires that they act appropriately once this diagnosis has been made. To facilitate this it might be helpful to have a named consultant in each hospital to take responsibility for ensuring that, in spite of frequent changes in staff, the doctors and nurses involved are fully informed about what to do, and where to get advice if they need it.

A practical aid would be a nationally approved check-list of the pre-conditions and the brain stem tests, which could act both as an *aide-memoire* for the clinician at the bedside, and as a permanent record to be filed in the patient's case-sheet. Guidelines for diagnosis are not, however, to be regarded as rigid rules—for such could not be written to meet every eventuality. Authorities publishing guidelines both in America (American Neurological Association, 1976) and in Britain (Conference of Medical Royal Colleges and their Faculties of the U.K., 1976a, b; Robson, 1981) have emphasized the importance of medical judgement in deciding, in individual cases, exactly what investigations are necessary, how long a period of observation is needed before the diagnosis of brain death can be made, and whether there are circumstances that allow for one or more tests being omitted. At the end of the day it is the doctor at the bedside who must decide when his patient is dead.

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CRYOANALGESIA: THE RESPONSE TO ALTERATIONS IN FREEZE CYCLE AND TEMPERATURE

P. J. D. EVANS, J. W. LLOYD AND C. J. GREEN

SUMMARY

One hundred and forty male rats received a cryoinjury to a segment of the exposed sciatic nerve. A variety of temperatures and freeze patterns was used and the recovery of function was monitored. Where obvious nerve freezing occurred, the cryoinjury caused complete loss of function in the limb. The return of motor activity was first noted at 25 days (mean) but complete return of motor activity and of pain sensation was noted after 38 days (mean). The findings were consistent with an axonal growth rate of 1 mm per day. The time taken for regeneration was independent of both the duration of freezing and the application of a repeat freeze cycle. The temperature attained by the nerve was, however, important. Where it remained greater than −20 °C the results were unpredictable, but below this temperature the interruption was prolonged and uninfluenced by greater reductions in temperature.

The local application of cold to provide a method of pain relief is not a new idea. It is reported that Hippocrates left the first written record (Jones, 1931). Unfortunately most attempts involved the use of ice, salt and water and in consequence have proved impractical except for the relief of surface pain. Cooper introduced the first cryoprobes capable of producing localized tissue freezing in 1961 (Garamy, 1968). Subsequently the possibility of freezing nerves deep to the body surface was realized. Prolonged analgesia could be obtained in patients suffering from chronic pain (Lloyd, Barnard and Glynn, 1976) and in those suffering acute postoperative pain (Glynn, Lloyd and Barnard, 1980). Lloyd named his technique cryoanalgesia.

The freezing of nerves, as with other tissues, is a physical process resulting in the formation of both intracellular and extracellular ice. The extent of cell destruction in an individual cryolesion will be dependent on many factors of which the rates of freezing and thawing as well as the temperature attained by the tissue are of great importance. It has been demonstrated that, once the nerve axons have been frozen, wallerian degeneration of the nerve will occur and recovery of function will depend primarily on the rate of axonal regrowth and the distance of the cryolesion from the end organ (Evans, 1981).

Clinically, the return of pain has not always mirrored this physiological observation. Although, in many patients, the return of sensation has been accompanied by a return of the previous degree of chronic pain, in others the duration of pain relief has greatly exceeded the period of sensory interruption (Barnard, Lloyd and Glynn, 1978). This intriguing clinical observation has never been explained satisfactorily. Denny-Brown and others (1945) demonstrated in animal studies that cooling to temperatures greater than 0 °C produced a disassociation in the interruption of nerve conduction; motor fibres ceased functioning first. In further experiments where nerves were frozen, it was shown that in those rats permitted to recover there was also some disassociation of the return of function, although this was unpredictable (Denny-Brown et al., 1945).

The present study was undertaken to assess what factors governed the extent of nerve damage in a cryolesion and whether alterations in the method of freezing had a significant effect on the quality or duration of the conduction block. More specifically, we wished to determine if the pattern of freezing influenced clinically the rates at which motor or sensory (pain) function returned. Three factors were studied: the temperature to which the nerve was frozen; the duration of tissue freezing; and the effect of a repeat freeze performed after a short interval during which the nerve was permitted to thaw.

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METHOD

One hundred and sixty male Sprague–Dawley rats, of mean age 3 months and weight 300 g, were anaesthetized with an inhalation mixture of 2% halothane in oxygen. The left sciatic nerve was exposed for a length of 2 cm through a posterior muscle-splitting incision of the gluteus maximus muscle. The nerve was mobilized from the surrounding tissues and marked with a 5.0-gauge silk suture before being frozen. A specially modified hooked ophthalmic cryoprobe was used to lift the nerve free of the tissues and the lesion was produced just proximal to the mark. The rats were divided into groups of 40 and received one of a number of different freeze–thaw cycles (table I).

TABLE I. *The various freeze sequences used in the four main study groups. Groups A, B, C and D were further subdivided into seven subgroups each of five rats, in which the cryolesion was produced at different temperatures (0, −10, −20, −30, −40, −50, −60 °C). An eighth subgroup acted as control*

Group	Freeze sequence
A	Two 3-min freezes with a thaw interval of 2 min
B	Two 1-min freezes with a thaw interval of 2 min
C	A single freeze of 3 min
D	A single freeze of 1 min

Within each group, subgroups of five rats had the cryolesion produced at the specific temperatures 0, −10, −20, −30, −40, −50 and −60 °C. The remaining five rats in each group acted as controls.

The return of motor function was assessed clinically by pulling the rat gently backwards by the tail across a smooth surface. Normally the leg extends and an attempt is made to grip the surface with the outstretched claws. In the denervated limb there is no activity and the limb hangs limply by the body. Function was graded 0 = no activity, partial = return of upper limb movement and complete = return of claw activity. Further confirmation of the return of full motor function was demonstrated by testing the ability of the rat to grasp and hold a rounded object in the hind paw. Both these tests gave good end-points within the limit of a few days.

Similarly, the return of sensation was tested by observing the response to a squeeze with an untoothed forceps applied across the proximal interphalangeal joint of the fourth toe. This point was used because occasionally a high division of the sciatic nerve meant that some branches were not included within the cryolesion and this resulted in incomplete anaesthesia of the first and second toes. Return was graded 0 = no activity, 1 = interest in the toe following the stimulus, but no attempt to draw away, and 2 = a squeak or other audible sound with a withdrawal or other protective reflex.

A number of rats were killed at strategic intervals during the recovery period and histological sections were made of the nerve at the site of injury and at proximal and distal sites. These were compared with normal nerve sections taken from the opposing limb. The results are the subject of a separate report.

APPARATUS

The localized nerve freezing was performed with a Spembly BMS 40 cryosurgical unit. The refrigerant was nitrous oxide gas which was delivered to the instrument through a variable flow valve at pressures between 10 and 60 $\mathrm{kgf\,cm^{-2}}$. The probe (fig. 1) was an ophthalmic model which had been modified by the addition of a silver tip containing a 2-mm notch in which the nerve could lie. Two chromel constantan thermocouples were incorporated into the tip, one on either side of the notch, and the tip temperature was recorded on a "Spembly Cryotemp" temperature meter. A positive defrost facility was also incorporated within the unit and this enabled the small quantities of tissue frozen to be completely thawed within a maximum of 10 s of the termination of the freeze cycle.

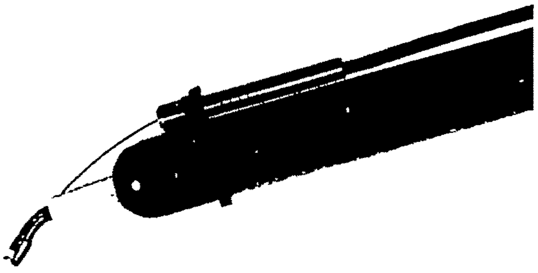

FIG. 1. Modified Spembly ophthalmic cryoprobe with silver tip containing 2-mm notch and two thermocouples.

Two-point measurement of the cryoprobe tip temperature enabled a record to be maintained of any gradient occurring across the substance of the tissue. In practice, because of the highly conductive silver tip and the small quantity of tissue frozen, the gradient was negligible and did not influence the response to the freeze injury.

Where the probe induced a visible freeze injury, the complete body of the nerve was involved and the lesion extended axially for a length varying from 4 mm at −20 °C to 11 mm at −60 °C. Those rats receiving a second freeze had the same segment refrozen.

RESULTS

This study investigated three principal aspects of the freeze injury. In all the rats studied the response to injury was judged by the measurement of the clinical return of motor and sensory function. None of the control rats, which had the sciatic nerve exposed and the cryoprobe applied without cooling, showed any loss of function upon recovery of anaesthesia or at any subsequent time. Of the remaining 140 rats, a further 22 (18.7%) failed to obtain sustained anaesthesia or suffered no consequences from the cryoinjury (table II). The rest suffered prolonged anaesthesia consistent with a period of axonal degeneration and regeneration.

TABLE II. *The overall results of the attempted cryoinjury to the sciatic nerve in the 140 rats studied*

Prolonged anaesthesia	122
Anaesthesia for up to 24 h	1
Motor loss (only) for 24 h	3
Sensory loss (only) for 24 h	3
No anaesthesia	11

Temperature

Following the freeze injury the majority of rats developed immediate sensory loss in the leg and foot. Overall the mean interval before the return of pain appreciation was 38 days (SD 14). Table III shows the mean values for the return of sensation in all the subgroups. The mean values for each of the main groups A, B, C and D were not significantly different ($P > 0.3$), but there was a marked difference between the mean values of the subgroups ($P < 0.01$ by Friedman two-way analysis of variance). This difference was further analysed by comparing the means, and it was found that where the temperature remained greater than −20 °C the duration of sensory loss was frequently short. At less than −20 °C the duration of sensory loss was invariably prolonged, but not further influenced by greater decreases in temperature.

TABLE III. *Mean interval (days) before a response was observed to painful stimulus applied to the hind paw of rats in which a segment of the sciatic nerve had been frozen at open exposure*

	Days before the return of sensation (mean value for each group of five rats)			
Temperature (° C)	Group A	Group B	Group C	Group D
−60	47.0	43.0	38.3	37.2
−50	50.8	43.6	44.4	40.8
−40	46.4	48.0	49.4	45.8
−30	31.2	40.4	39.0	43.0
−20	45.0	40.0	31.6	48.0
−10	19.6	31.8	5.6	0.0
0	8.6	8.6	2.8	0.0
Control	Sensation normal in all rats upon recovery from anaesthesia			

The return of motor activity to the hind limb was first observed in the thigh muscles (partial motor) after an interval of 24.5 days (SD 7.3) whilst the return of full power to the paw was noted after 37.9 days (SD 14) (table IV). These findings were consistent with an axonal growth rate of between 1 and 1.2 mm per day. Again there was no difference between the means of the main groups ($P = 0.05$), but a significant difference between the means for the subgroups ($P < 0.01$; Friedman two-way analysis of variance). Analysis of this effect of temperature showed that rats which received a freeze injury at more than −20 °C had significantly shorter periods of interruption of motor response than those in which the freeze injury was at or less than −20 °C. Further decreasing of the temperature, however, did not increase the period taken for the return of function (fig. 2).

The results for return of complete motor activity and those for the return of sensation were compared using a paired t test. No significant difference between them was found.

Duration of freezing

Rats from groups A and C received freeze injuries of 6 and 3 min duration respectively. No differences could be detected in the time taken for the return of either motor or sensory function where the results for the freeze injuries at −20 °C or less were compared with the equivalent

TABLE IV. *Mean interval (days) before the return of motor activity was observed in the hind limbs of groups of rats the left sciatic nerves of which had undergone localized cooling, at specific temperatures, to cause a freeze injury*

	Days before return of motor activity in thigh (P) and paw (C) of hind limb							
	Group A		Group B		Group C		Group D	
Temp. (°C)	P	C	P	C	P	C	P	C
−60	25.0	47.5	27.0	42.7	27.3	37.4	26.0	40.0
−50	21.0	49.2	22.0	44.3	27.0	43.4	20.6	33.6
−40	31.8	51.2	24.6	45.8	29.8	43.2	30.0	48.2
−30	25.4	40.4	21.0	37.6	22.6	38.0	24.6	45.8
−20	30.4	49.4	28.5	44.0	22.4	33.6	33.0	42.8
−10	17.6	39.8	16.5	36.8	4.6	7.8	0.0	0.0
0	7.2	9.0	1.0	2.0	0.0	2.6	0.0	0.0
Control	On recovery from anaesthesia no rat showed any evidence of motor loss							

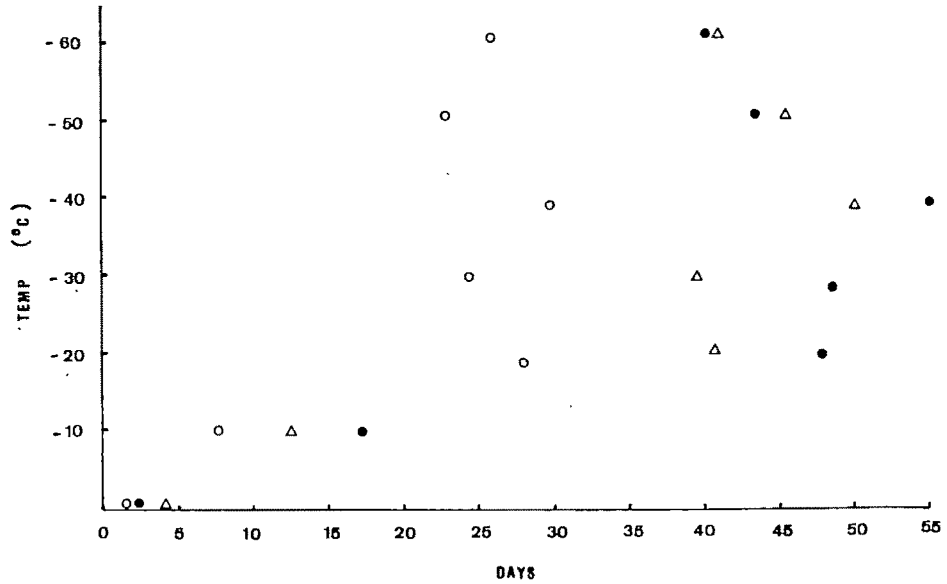

FIG. 2. Combined data for rats from all the freeze groups, demonstrating that decreasing the temperature did not cause a progressive increase in the time taken for return of nerve function. Each series of points (○ = partial motor; ● = complete motor; △ = sensory), at the indicated temperatures, represents the mean of 20 rats. Five from each of the four freeze groups: A = two 3-min freezes; B = two 1-min freezes; C = a 3-min freeze and D = a 1-min freeze. The return of function was expressed as *partial motor*, indicating return of power to the thigh muscles, *complete motor*, indicating return of claw grip and *sensory*, indicating the return of pain appreciation to the paw. Below −10 °C the temperature attained by the nerve was not related to the time taken for regeneration.

observations for those rats which received 1- or 2-min freeze (paired *t* test). The subgroups for 0 and −10 °C (in which it might be expected that prolonged freezing would increase the chance of axonal degeneration occurring) were compared separately. Using chi-square tests, the number of rats which regained partial motor response in less than 24 h was compared with the number which took longer to recover. It was found that the duration of the freeze had a marked effect on the number of days to recover ($P < 0.01$). The same was true for the complete motor response, but not for the sensory response.

Repetition of the freeze cycle

All the rats in groups A and B received a second freeze at the same site on the sciatic nerve immediately following a thaw interval which lasted 2 min. When the results for these two groups were compared with the results from those rats which received a single freeze, the return of motor and sensory function proved to be similar (paired t test). However, when chi-square analysis was used to compare the number of rats gaining return of function within 24 h *v.* a longer period of interruption, it was found that, for the critical subgroups of 0 and −10 °C, those rats which received a repeat freeze were more likely to have a longer interruption of partial motor, complete motor and sensory function (respective P values <0.0005, <0.001 and <0.001)

DISCUSSION

Our studies, like those of others (Douglas and Malcolm, 1955; Gaster et al., 1971; Menz, 1971; Carter et al., 1972; Beazley, Bagley and Ketcham, 1974; Lenz, 1974; Whittaker, 1974a), confirm that a freeze injury produced in peripheral nerves causes a prolonged but reversible interruption of conduction, the duration of which is largely dependent on the rate of axonal regrowth and the distance of the cryolesion from the respective end-organ. This is demonstrated by the fact that return of motor activity to the thigh muscles (partial motor), occurred approximately 15 days before motor activity was observed in the paw (complete motor). The mean axonal growth rate was 1.2 mm per day. Similar growth rates have been reported by both Gaster and others (1971) and Beazley, Bagley and Ketcham (1974). These workers also demonstrated that there was no difference clinically in the period of motor or sensory nerve fibre interruption and this has been confirmed in the present study. Denny-Brown and co-workers (1945) suggested that motor fibres were more sensitive to cold injury and took longer to recover, but in a number of his experiments temperatures close to 0 °C were used, and it is likely that in some cases they were observing the effects of a partial nerve injury short of freezing.

The mechanism of freeze injury has been closely studied by Joy and Finean (1963), Menz (1971), Carter and others (1972) and Whittaker (1974b), each of whom concluded that the major factors involved were the development of intra- and extracellular ice crystals. Ice either caused gross shifts in tissue osmolarity and cell wall permeability or produced physical disruption of the myelin sheath and Schwann cell from the formation of large ice crystals. More recently, Heckman and others (1980) suggested that extensive vascular damage causing macromolecular and cellular extravasation is an important factor. Consequently, the cryoinjury remains an essentially physical process and, once ice crystal formation has produced destruction of the nerve, no additional benefit will be achieved by further decreasing of the temperature, although it is quite obvious that the less the temperature the larger will be the size of the cryolesion and length of nerve involved.

There is a minimum size for a cryolesion, as it is possible for myelinated fibres still to conduct even though small segments of the axon are inactive. The impulse appears to hurdle the inactive area but, as Douglas and Malcolm (1955) demonstrated in cats, an injury of 3–6 mm in length is sufficient to stop saltatory conduction. In this study the visible lesion of 4 mm was always effective and although it is difficult to estimate in man the length of the cryolesion required to inhibit impulses, it is obvious that the size of the cryolesion is one of the important factors governing the success of treatment.

Our results demonstrated that the time taken for nerve recovery was no different for the rats which received a cryoinjury at −20 °C than those which received one at −60 °C. Similarly, the effects of cycle repetition and prolonging the freeze duration produced no additional benefit. However, these factors may be of considerable importance in clinical practice, for example where the nerve is not exposed and proximity to the probe can only be estimated.

As with other biological tissues, freezing of nerve does not occur at 0 °C, but at temperatures as low as −10 °C (Denny-Brown et al., 1945; Gaster et al., 1971; Menz, 1971; Carter et al., 1972). This may explain the unpredictable effects observed in those rats in which temperature reduction was limited to between 0 and −20 °C. In some of these cooling merely resulted in a short interruption of conduction consistent with a neuropraxia rather than axonal destruction. It was possible to demonstrate, within this critical temperature range, that prolonging the freeze time or repeating the cycle did enhance the injurious effect of freezing. Admittedly this was of limited value, as the nerve was exposed and the freeze temperatures were close to 0 °C, but as cryoanalgesia is frequently used as a percutaneous technique the value of both these factors becomes more important. For instance, to provide pain relief for intercostal neuralgia the probe is inserted so that the tip lies adjacent to the lower border of the rib and as near the nerve as possible, although frequently the probe is not abutting the nerve and in consequence increased success is likely if a large cryolesion is produced. In practice the size of the lesion created will be dependent on the probe temperature, the duration of freezing and repetition of the freeze cycle (Evans, 1981). Therefore, if the probe is not closely applied to the nerve, increasing any or all of these factors will lead to an enlarged cryolesion which may well encompass a nerve which would not otherwise have been included in the area of cell destruction.

Hannington-Kiff (1980) has suggested that the duration of conduction interruption can be predicted by controlling the temperature of the freeze injury and that a temperature of −20 °C will briefly interrupt conduction, adequately for postoperative pain. Our study confirmed that decreasing the temperature of the nerve to between 0° and −20 °C frequently resulted in brief interruption, but it was certainly not predictable.

Cryoanalgesia is a new approach to producing nerve blockade and may well confer advantages over other techniques. Brief interruption of conduction can be produced with local anaesthetic drugs and, although these agents are primarily used to provide surgical anaesthesia, they are sometimes successful in relieving intractable pain, perhaps by breaking an established "cycle of pain". More prolonged anaesthesia can usually be obtained only by destructive means. Nerve crushing or section will produce a complete loss of function, but subsequent axonal growth may lead to neuroma formation and inadequate return of activity (Bradley, 1975). Neurolytic agents such as phenol and alcohol often fail to kill all the fibres within a nerve and can cause chronic neuritis which is frequently more troublesome than the patient's original pain. Consequently these agents should not be used for the interruption of peripheral nerve conduction. Radiofrequency heat destruction is also used to produce interruption of nerve conduction and although it is possible to destroy pain fibres selectively by the control of tissue temperature (Sweet and Wepsic, 1974), the temperature range between selective fibre destruction and complete destruction is narrow (1.5 °C). The lesion is not reversible and neuroma formation may occur. In contrast, a cryolesion is reversible and has not been associated with neuromata. Indeed, in our studies none of the rats showed any evidence of neuroma formation at necropsy and fibrosis and scarring at the site of injury was minimal.

In conclusion, a predictable nerve injury can be produced by local cooling to at least −20 °C with consequent prolonged but reversible interruption of conduction without tendancy to neuroma formation or to chronic neuritis.

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CRYOANALGESIE : REACTION AUX MODIFICATIONS DU CYCLE DE CONGELATION ET A LA TEMPERATURE

RESUME

On a infligé une blessure cryogène à un segment du nerf sciatique exposé de cent quarante rats mâles. On a utilisé une variété de températures et de modèles de congélation, puis on a surveillé la reprise des fonctions. Partout où il s'est produit une congélation évidente du nerf, la blessure cryogène a causé la perte complète de la fonction du membre. Le retour de l'activité motrice a été en premier lieu remarqué 25 jours plus tard (en moyenne), mais le retour complet de l'activité motrice et de la sensation de douleur n'a été noté que 38 jours après (en moyenne). Ces constatations ont été en rapport avec une cadence de croissance de l'axone de 1 mm par jour. Le temps qu'il a fallu pour la régénération a été indépendant de la durée de la congélation et de l'application d'un second cycle de congélation. La température supportée par le nerf a cependant eu son importance. Lorsque celle-ci est restée supérieure à −20 °C les résultats ont été imprévisibles, mais au-dessous de cette température l'interruption a été prolongée et n'a pas été influencée par les plus fortes réductions de température.

KALTEANALGESIE: REAKTION AUF ÄNDERUNGEN IM GEFRIERZYKLUS UND DER TEMPERATUR

ZUSAMMENFASSUNG

140 männliche Ratten erheilten eine Kälteverletzung des freigelegten Ischiasnervs. Mehrere Temperatur- und Gefrierverfahren wurden verwendet, und die Funktionserholung wurde überwacht. Wo es zu klarer Nerveneifrierung kam, wurde dadurch vollkommener Funktionsverlust des Gliedes bewirkt. Motorische Aktivität kehrte zuerst nach 25 Tagen (im Schnitt) wieder, aber völlige Rückkehr und auch Wiederkehr der Schmerzempfindlichkeit wurde nach 38 Tagen (im Schnitt) beobachtet, was einer Neuritwachstumsrate von 1 mm pro Tag entspricht. Regenerationszeit war unabhängig von Gefrierdauer und einem wiederholten Gefrierzyklus. Wichtig war aber die Nerventemperatur—blieb sie über −20 °C waren die Resultate unvorhersehbar, doch unter dieser Temperatur war die Unterbrechung verlängert, und nicht beeinflusst von grösseren Temperaturverringerungen.

CRIOANALGESIA: RESPUESTA A LAS ALTERACIONES EN EL CICLO DE CONGELACION Y EN LA TEMPERATURA

SUMARIO

Se sometieron ciento cuarenta ratones a heridas producidas por congelación en un segmento del nervio ciático expuesto. Se usaron una variedad de temperaturas y de configuraciones de congelación, vigilándose la función de la recuperación. Allí donde tuvo lugar una evidente congelación del nervio, la herida ocasionada por la congelación provocó la pérdida total de la función del miembro. La recuperación de la actividad motriz se apreció por primera vez a los 25 dias (media), pero la recuperación total de tal actividad motriz y la sensación de dolor se apreciaron después de transcurridos 38 dias (media). Los resultados fueron consistentes con un régimen de crecimento axónico de 1 mm por dia. El tiempo necesario para la regeneración fue independiente tanto de la duración de la congelación como de la aplicación repetida de un ciclo de dicha congelación. La temperatura alcanzanda por el nervio fue, sin embargo, importante. Allí donde permaneció superior a los −20 °C, los resultados fueron impredecibles, pero por debajo de esta temperatura, la interrupción se prolongó y no quedó afectada por las posteriores reducciones en la temperatura.

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SELECTIVE HYPOPHYSECTOMY FOR METASTATIC PAIN

A review of ethyl alcohol ablation of the anterior pituitary in a Regional Pain Relief Unit

J. W. LLOYD, W. A. L. RAWLINSON AND P. J. D. EVANS

SUMMARY

Selective adenohypophysectomy, by the injection of up to 1 ml of absolute alcohol to the pituitary gland, was used to produce pain relief in 25 patients suffering from metastatic cancer. Thirty-five treatments were given and good analgesia was obtained in 74%. The median duration of pain relief was 6–7 weeks, although some treatments produced relief for up to 20 months. The procedure was most successful in relieving bone pain in patients with advanced carcinoma of the breast or prostate. The use of a fine-gauge needle for the intranasal trans-sphenoidal approach to the gland and the injection of alcohol to the anterior part (pars distalis) of the gland reduced the frequency of the major complications diabetes insipidus (17%) and prolonged visual disturbance (3%).

The method of pituitary destruction by absolute alcohol in the treatment of painful metastases from hormone-dependent cancers was developed by Moricca (1970, 1973, 1974a,b) after earlier workers had described various hormone-subtraction therapies as partially successful in controlling (but not providing analgesia for) the growth of the tumours. The purpose of the present study was to assess retrospectively the efficacy and problems of the technique as used in the Oxford Regional Pain Relief Unit in the 3 years since its introduction.

PATIENTS

Twenty-five patients with metastasizing cancers have undergone the technique of alcohol hypophysectomy at the Unit since the first procedure was performed in December 1977. Thirteen were women with primary carcinoma of breast and nine were men with primary prostatic tumours. There was also one man with primary carcinoma of bronchus, one with primary teratoma of testis, and one woman with a primary carcinoma of the sigmoid colon.

Thirty-five hypophysectomies were performed. Two patients had the procedure repeated, one received three injections and two received a total of four. The mean age of patients at the time of treatment was 59.8 yr (range 29–77 yr), although patients with prostatic cancer were slightly older (mean 67.7 yr).

Patients were considered for hypophysectomy if they met certain criteria: they suffered from bone pain and had obvious skeletal deposits, had previously shown evidence of a symptomatic response to hormone therapy, had a reasonable prognosis in terms of anticipated survival and had a long interval from the diagnosis of the primary tumour to the development of pain.

In any individual, the evaluation of these criteria was inevitably subjective, and part of the purpose of the study was to assess retrospectively how far these requirements had been met. The time and indications for referral to the unit also varied. This was inevitable in a regional unit taking patients from hospitals and general practitioners.

METHOD

Light general anaesthesia was always administered to the patients before hypophysectomy. The vocal cords were sprayed with lignocaine before endotracheal intubation so that the anaesthetic might be maintained solely with nitrous oxide and oxygen during the critical period towards the end of the procedure when the alcohol was injected. The throat was packed with ribbon gauze and both nostrils were prepared with 25% cocaine paste to produce local anaesthesia and vasoconstriction.

A single 16-gauge needle with introducer was passed through one nostril to enter the pituitary fossa via the transphenoidal route, as described by Moricca (1977). Bi-plane image

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intensification was used to monitor the needle's progress, and the introducer was positioned so that it was just within the bony margins of the anterior part of the pituitary fossa. A 20-gauge needle was then passed through the introducer so that it entered 2–3 mm into the substance of the gland (pars distalis). An injection of iophendylate 0.1 ml (Myodil, Glaxo) was used to confirm the position of the needle in the body of the gland. Absolute alcohol 0.8–1.0 ml was instilled to the pituitary fossa, in 0.1-ml increments over 10–15 min, and at this stage the general anaesthetic was lightened so that any movements or dilatation of the pupils could be detected.

The patients stayed in hospital for at least 48 h following the procedure, to determine the efficacy in terms of pain relief (patient's evaluation), requirements for analgesic drugs, and to monitor the development of complications such as diabetes insipidus. Replacement steroid therapy was instituted routinely, in the form of cortisone acetate 25 mg twice daily, to those patients not already receiving corticosteroids. Patients have then been reviewed at 6-weekly intervals.

The success of the procedure was determined by the patients' subjective evaluation of pain relief and by their requirement for analgesics. Patients who obtained good relief had either no pain or slight pain after treatment, required only mild analgesics for symptom control or had a significant reduction (>50%) in their narcotic analgesic consumption. Those patients who were considered to have a poor result from the procedure had little in the way of pain relief and had no change in their analgesic requirements.

RESULTS AND COMPLICATIONS

Good analgesia was obtained following 74% of hypophysectomies performed (table I). In those patients suffering from carcinoma of the breast the results were better (79%). The three injections carried out on patients with bronchial, colonic or testicular tumours were unsuccessful in producing analgesia. The hormone-insensitive tumours have been withdrawn from the statistics and no more hypophysectomies are planned for similar patients in future.

Figure 1 shows the duration of analgesia obtained following hypophysectomy. It proved difficult to assess completely as a number of patients who were pain-free on discharge died (Nos 6, 8, 13, 23, 24) or failed to attend the follow-up appointments (Nos 2, 3, 5, 10). Median duration of pain relief was 6–7 weeks. Thirteen of the 31 (42%) hypophysectomies completed on the patients with breast or prostatic tumours still produced analgesia at 6 weeks. Two patients (Nos 14, 25) are still being followed up, having obtained adequate analgesia from their most recent hypophysectomy.

TABLE I. *Analgesia from 34 completed hypophysectomies*

		Good analgesia	Poor analgesia
Total treatments	34	25 (74%)	10
Primary tumour:			
breast	19	15 (79%)	4
prostate	12	9 (75%)	3
testis	1	0	1
colon	1	0	1
bronchus	1	0	1

Table II shows the complications, arbitrarily divided into major and minor complications. Only one procedure had to be abandoned, because of a major haemorrhage, but this produced no permanent disturbance and the patient underwent two further successful hypophysectomies. The frequency of headache (17% of all attempts) and nausea (9%) was relatively small. The frequency of diabetes insipidus was 17% (six treatments) and these were mainly among the early treatments in the series. Only four patients required vigorous anti-diuretic hormone therapy.

Histological examination of the pituitary gland was possible in three patients (Nos 4, 11, 17). In two, there was minimal evidence of gland destruction and in the one patient where the damage was obvious (No. 11) no relief of pain had been obtained from the procedure.

DISCUSSION

In 1953 Luft and Olivecrona described surgical ablation of the pituitary gland in the treatment of metastases from hormone-dependent tumours, with a view to reducing the spread of the disease rather than specifically for analgesia. Since then Moricca (1970, 1973, 1974a, b) has devised a method of ablation using alcohol instilled directly to the pituitary. This method has a number of advantages as a simple, safe and inexpensive procedure, which can, if necessary, be repeated a number of times without requiring specialist neurosurgery and a long stay in hospital. The

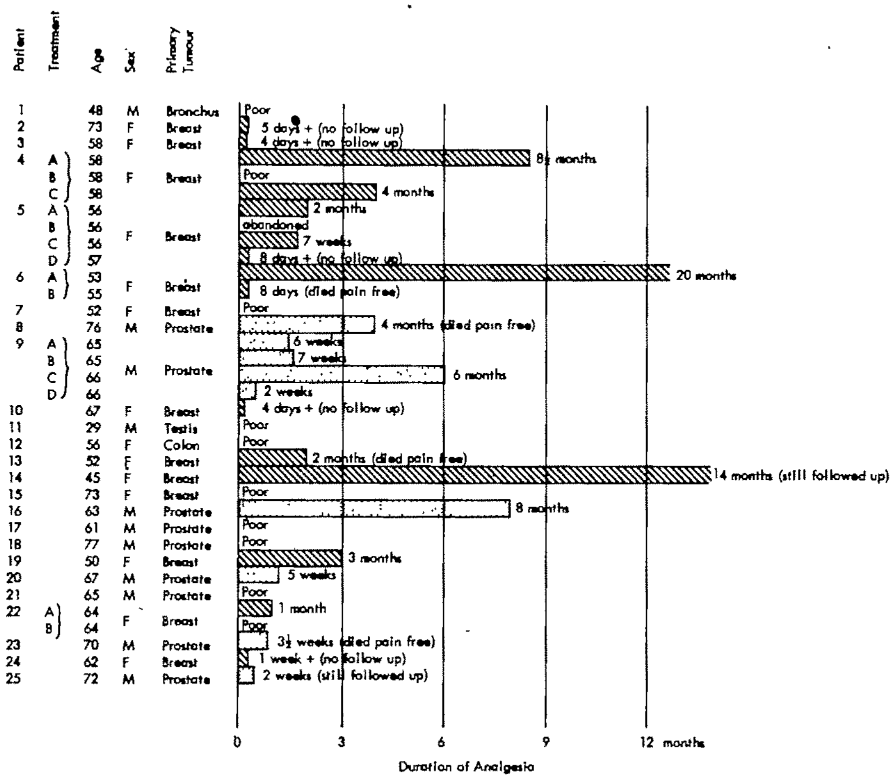

FIG. 1. Patients, primary tumours and durations of analgesia for 35 treatments in 25 patients.

TABLE II. *Complications produced in 35 attempted hypophysectomies*

Complications	No.
Major	
Major bleed (abandoned procedure)	1
Loss of visual field	1
Diabetes insipidus	6 (17%)
Myxoedema	1
Minor	
Headache	6 (17%)
Vomiting/nausea	3 (9%)
Temporary pupil change	3 (9%)
Leak of c.s.f.	2 (6%)
Epistaxis	1

technique as practised in the Oxford Regional Pain Relief Unit at Abingdon is carried out with a single injection, applicable to an analgesic method performed by anaesthetists.

The aim of the technique reported by previous workers (Corssen et al., 1977; Moricca, 1977; Lipton, 1978; Lipton et al., 1978) has been total pituitary ablation, and the volumes of absolute alcohol used have generally been larger than those in the present series. Corssen and others (1977) described 1–2 ml, Moricca (1977) used 0.6–2.0 ml and Lipton (1978) 1 ml. Our own aim has been selective anterior hypophysectomy, using absolute alcohol 0.8–1.0 ml with the needle tip just within the body of the adenohypophysis. Consequently, our frequency of diabetes insipidus is lower (17%) than those quoted by Moricca ("very frequent") and Lipton ("most, but rarely extreme"), and our figures improved as the number increased. The most distressing complication for patients was the development of visual disturbance. This occurred infrequently but, in retrospect, was found to have resulted when there was failure of the needle to enter the substance of the adenohypophysis or where the rate of alcohol injection had been too rapid.

Our success in terms of analgesia is comparable to that of other series using alcohol ablation of the pituitary. Seventy-four percent had significant pain relief, with 48% of the treatments that provided analgesia for breast or prostatic cancers lasting at least 6 weeks. Corssen and others (1977) described complete relief in 54% of 24 patients, plus some analgesia in a further 42%. Lipton and others (1978) described complete relief from 41% of 155 injections with a median duration of 4 months of analgesia from the successful injections. Our series includes good relief in 80% of 31 injections, with a median duration of 2 months from the 17 successful injections that have been followed up beyond 2 weeks.

Our success rate is also comparable to that of other workers using different methods of hypophysectomy. Gye and others (1979) used cryohypophysectomy in 22 patients with metastatic breast cancer and obtained pain relief for 3 months in 55% of the cases.

The mechanism of pain relief following hypophysectomy remains uncertain, but it has been suggested that part of the effect may be a result of the spread of alcohol via the pituitary stalk into the hypothalamus, thereby directly causing fixation with alcohol, or indirectly causing thrombosis and infarction (Miles and Lipton, 1976; Moricca, 1977; Yanagida et al., 1979; Williams et al., 1980). Although we have no clear evidence to confirm this hypothesis, a number of points are in its favour. At the time of injection contrast was seen to track up the pituitary stalk in most of hypophysectomy procedures; the destruction of the pituitary gland assessed by measurement of pituitary hormone production could not be related to the frequency and degree of analgesia (authors' personal observation) and two patients who had complete relief of symptoms had little evidence of adenohypophyseal destruction postmortem.

We consider that the technique described above, of selective adenohypophysectomy with a small volume of absolute alcohol, is a valuable method of providing analgesia in patients with terminal cancer in whom the tumour is demonstrably hormone-sensitive, and where bony metastases are causing unbearable pain. It is a relatively quick and simple method involving as little confinement to hospital, discomfort and surgical intervention as possible in patients with limited life expectancy.

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HYPOPHYSECTOMIE SELECTIVE POUR LES DOULEURS METASTATIQUES

Revue des ablations effectuées sous alcool éthylique de la glande pituitaire antérieure dans une unité régionale de soulagement de la douleur

RESUME

On a utilisé l'adénohypophysectomie sélective par l'injection d'alcool absolu (jusqu'à 1 ml) dans la gland pituitaire, pour soulager la douleur de 25 patients souffrant d'un cancer métastatique. On a administré trente-cinq traitements et obtenu une bonne analgésie dans 74% des cas. La durée moyenne du soulagement de la douleur a été de 6 à 7 semaines, bien que dans certains cas on ait obtenu un soulagement pendant une péroide allant jusqu'à 20 mois. Ce procédé a été particulièrement efficace pour le soulagement de la douleur dans les os chez les patients atteints d'un carcinome avancé du sein ou de la prostate. L'usage d'une aiguille de petit calibre pour l'injection intranasale transphénoïde de la glande et l'injection d'alcool dans la partie antérieure de la glande (pars distalis) a réduit la fréquence des principales complications: diabète insipide (17%) et perturbations visuelles prolongées (3%).

SELEKTIVE HYPOPHYSENEXTIRPATION GEGEN METASTATISCHE SCHMERZEN

Ein Überblick über die Äthylalkohol-Ablation der vorderen Hypophyse bei einer regionalen Schmerzenslinderungsklinik

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ZUSAMMENFASSUNG

Selektive Adenohypophysenextirpation durch Injizierung von bis zu 1 ml absoluten Alkohol in den Hypophyse wurde angewandt, um bei 25 an metastatischem Krebs leidenden Patienten eine Schmerzenslinderung zu bewirken. Es wurden 35 solche Behandlungen durchgeführt, und bei 74% wurde eine gute Analgesie erreicht. Die mittlere Dauer der Linderung betrug 6–7 Wochen, obwohl bei einigen Patienten die Linderung bis zu 20 Monaten dauerte. Das Verfahren hatte seinen grössten Erfolg bei der linderung von Knochenschmerzen bei Patienten mit fortgeschrittenem Brust- oder Prostatakrebs. Die Anwendung einer dünnen Hohlnadel für den intranasalen transsphenoidalen Zugang zu der Hypophyse und die Injizierung des Alkohols in den vorderen Teil (pars distalis) bewirkte eine Abnahme der Frequenz von ernsthaften Komplikationen wie Diabetes insipidus (17%) und ausgedehnten Sehstörungen (3%).

HIPOFISECTOMIA SELECTIVA PARA EL DOLOR METASTATICO

Revisión del ablación de la pituitaria anterior mediante alcohol etilico en una unidad local de mitigación del dolor

SUMARIO

Se usó adenohipofisectomía selectiva para producir la mitigación del dolor en 25 pacientes que sufrían de cáncer metastático, efectuándose esto mediante la inyección de hasta 1 ml de alcohol anhidro dentro de la glándula pituitaria. Se administraton treinta y cinco tratamientos y se obtuvo una buena analgesia en el 74%. La duración media de la mitigación de dolor fue de 6 a 7 semanas, aunque algunos tratamientos produjeron mitigación por periodos que llegaron a los 20 meses. El procedimiento alcanzó su máximo éxito en la mitigación del dolor de heusos en aquellos pacientes con carcinoma avanzado del pecho o de la próstata. El uso de una aguja fina para el recorrido transfenoidal del curso intranasal, hasta llegar a la glándula, y la inyección del alcohol en la parte anterior (pars distalis) de la glándula, redujo la frecuencia de las principales complicaciones de la diabetes insipidus (17%) y de la perturbación visual de gran duración (3%).

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ALVEOLAR GAS RELATIONSHIPS DURING USE OF THE CIRCLE SYSTEM WITH CARBON DIOXIDE ABSORPTION

C. M. CONWAY

SUMMARY

Expressions have been derived to show the dependence of alveolar oxygen and anaesthetic concentrations on fresh gas flow to a circle system, the composition of fresh gas, ventilation and gas uptake. The form of these expressions is influenced by the degree of mixing of fresh and expired gases within the circle system. These expressions assume an equilibrium state within the circle system and the rate at which equilibrium will be approached has been quantified in terms of the time-constants of change of composition of gas within the system. Time-constants approach infinity as fresh gas flow approaches values which just satisfy gas uptake. Whilst simplifying assumptions made in the derivation of the various alveolar gas equations limits their accuracy, the expression can serve as a guide to the likely behaviour of circle systems under any given conditions of use.

Circle systems with carbon dioxide absorbers are used with a variety of fresh gas flows. At one extreme, oxygen and anaesthetic gases can be supplied to the system in amounts equal to the uptake requirements of the subject. Under these circumstances no gas should be vented from the system. Alternatively, the amounts of oxygen and anaesthetic gases in the fresh gas supply may exceed uptake requirements to any desired extent. When the system is totally closed or when the components of fresh gas only slightly exceed uptake requirements, the system has the virtue of economy, but under these circumstances variations in gas uptake by the subject may greatly influence the composition of gas within the system and inhaled by the subject. As fresh gas flow to a circle system increases, gas uptake has a diminishing effect on inspired gas composition, but the virtue of economy is lost.

Several workers have produced theoretical analyses of the behaviour of circle systems (Foldes, Ceravolo and Carpenter, 1952; Fitton, 1958; Eger, 1974; Virtue, 1974; Holmes and Spears, 1977; Lowe, 1979). The majority of these analyses have concentrated upon the effects of varying fresh gas flow and composition upon inspired gas concentration. Mapleson (1960) derived expressions showing the alveolar concentration of anaesthetics during use of a circle system. His expressions require a knowledge of mixed venous anaesthetic content. In the present study the effects of variations in fresh gas flow and anaesthetic uptake upon alveolar gas composition are described by means of expressions which do not invoke knowledge of venous anaesthetic concentrations.

Assumptions

It is assumed that all carbon dioxide exhaled by the subject is totally absorbed within the system. When gas is vented from the system this is assumed to occur after carbon dioxide absorption. A simple two-compartmental lung model is used, consisting of an alveolar space and a deadspace. Expired gas is considered to exist at BTPS at 37 °C, gas uptakes are considered at STPD and fresh gas is considered to be at ATPD at 20 °C. All gas uptakes are considered to have constant values.

In most of the analyses it is assumed that gases are supplied to the system in excess of uptake requirements, and that some gas is vented from the system. It is also assumed that oxygen and anaesthetic agents in fresh gas are never supplied at rates below the oxygen and anaesthetic gas uptakes. The totally closed system with an exact balance between supply and demand of oxygen and non-metabolic gases is considered as a limiting case of the above approach.

Nomenclature

Standard nomenclature is used with the addition of the following terms:

$\dot{V}_F$ = Fresh gas flow
$\dot{V}_V$ = Mean vented gas flow

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$\dot{V}\mathrm{AN}$ = Non-metabolic gas uptake
$F\mathrm{F}_{\mathrm{O}_2}$ = Fresh gas oxygen concentration
$F\mathrm{S}_{\mathrm{O}_2}$ = Vented gas oxygen concentration
$F\mathrm{M}_{\mathrm{O}_2}$ = Oxygen concentration within the circle system

Other terms are defined where they arise in the analyses.

Black box analogy

A convenient starting point in this analysis is to consider a circle system attached to a subject as a black box, and to examine the way in which it influences an input of fresh gas when a steady state of gas uptake exists. The central box of figure 1 represents a circle system which received a fresh gas input, $\dot{V}\mathrm{F}$, of known flow and composition.

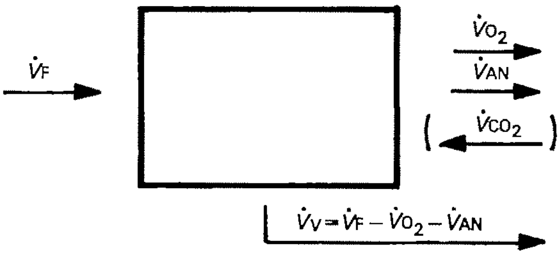
$\dot{V}\mathrm{F}$
$\dot{V}\mathrm{O}_2$
$\dot{V}\mathrm{AN}$
$\dot{V}\mathrm{CO}_2$
$\dot{V}\mathrm{V} = \dot{V}\mathrm{F} - \dot{V}\mathrm{O}_2 - \dot{V}\mathrm{AN}$

FIG. 1. The circle system as a black box. The central box here represents a circle system, to which is supplied a flow of fresh gas, $\dot{V}\mathrm{F}$. Through the medium of ventilation, oxygen and anaesthetic are removed from the system. Carbon dioxide is added but is assumed to be fully absorbed. The flow of gas vented from the system, $\dot{V}\mathrm{V}$, is in these circumstances equal to the difference between supplied and removed gas flows.

Through the medium of ventilation oxygen is removed from the system at a flow $\dot{V}\mathrm{O}_2$ and anaesthetic gases at a flow $\dot{V}\mathrm{AN}$. It is convenient to include nitrogen in this anaesthetic or non-metabolic uptake, noting that nitrogen uptake will usually have a negative sign. Carbon dioxide is added to the system at a flow $\dot{V}\mathrm{CO}_2$ and it is assumed that all added carbon dioxide is absorbed. If the components of fresh gas are supplied at rates in excess of their uptake, then some gas will be vented from the system. If the end expiratory volume of the system is constant, the mean flow of vented gas, $\dot{V}\mathrm{V}$, will equal fresh gas flow minus net gas uptake (here defined as the algebraic sum of all gas uptakes with the exception of $\dot{V}\mathrm{CO}_2$). Thus:

$$\dot{V}\mathrm{V} = \dot{V}\mathrm{F} - \dot{V}\mathrm{O}_2 - \dot{V}\mathrm{AN}.$$

The amount of oxygen in vented gas will at equilibrium be determined by the difference between the oxygen content of fresh gas and oxygen uptake. Oxygen concentration in vented gas, $F\mathrm{S}_{\mathrm{O}_2}$, can be expressed as:

$$F\mathrm{S}_{\mathrm{O}_2} = \frac{\text{oxygen content of fresh gas minus oxygen uptake}}{\text{fresh gas flow minus net gas uptake}}$$

or, stated algebraically:

$$F\mathrm{S}_{\mathrm{O}_2} = \frac{\dot{V}\mathrm{F}F\mathrm{F}_{\mathrm{O}_2} - \dot{V}\mathrm{O}_2}{\dot{V}\mathrm{F} - \dot{V}\mathrm{O}_2 - \dot{V}\mathrm{AN}} \qquad (1)$$

Oxygen concentration within the system may be equal to $F\mathrm{S}_{\mathrm{O}_2}$. It can always be expressed in terms of $F\mathrm{S}_{\mathrm{O}_2}$. This oxygen concentration of vented gas (which can be measured easily) will be shown to form a useful basis for a series of equations to define alveolar gas concentrations.

It will be noted that equation (1) contains no terms which directly invoke ventilation or gas disposition and mixing within the system. In the presence of complete carbon dioxide absorption alveolar carbon dioxide concentration, $F\mathrm{A}_{\mathrm{CO}_2}$ will depend only upon $\dot{V}\mathrm{CO}_2$ and alveolar ventilation and will not be influenced by the behaviour of the system. There are a large number of different possible geometrical arrangements of the components of a circle system and for any single arrangement an infinite number of different patterns of gas disposition may occur. To simplify the present analysis, two specific cases of gas disposition will be considered and a general formula then deduced.

Total gas mixing

The simplest form of gas disposition to be considered occurs when it is assumed that all fresh and expired gases entering the circle system form a uniform gas mixture. Inspired gas and vented gas will have the same composition as this mixture and thus the oxygen concentration of the mixture within the system, $F\mathrm{M}_{\mathrm{O}_2}$, will be the same as $F\mathrm{S}_{\mathrm{O}_2}$ as defined in equation (1). The oxygen concentration of the mixture in the system can also be defined in terms of its components. The system will receive per unit time fresh gas at a flow $\dot{V}\mathrm{F}$ and an oxygen concentration $F\mathrm{F}_{\mathrm{O}_2}$, and expired gas. Expired gas, $\dot{V}\mathrm{E}$, will undergo a volume decrement as a result of carbon dioxide absorption and its net contribution will be equal to $\dot{V}\mathrm{E} - \dot{V}\mathrm{CO}_2$. Expired gas will consist of a deadspace fraction, $\dot{V}\mathrm{D}$, with an oxygen concentration equal to $F\mathrm{S}_{\mathrm{O}_2}$, and an alveolar portion, $\dot{V}\mathrm{AE}$, with an oxygen concentration $F\mathrm{A}_{\mathrm{O}_2}$. Thus:

$$(\dot{V}\mathrm{F} + \dot{V}\mathrm{E} - \dot{V}\mathrm{CO}_2)\cdot F\mathrm{S}_{\mathrm{O}_2} = \dot{V}\mathrm{F}\cdot F\mathrm{F}_{\mathrm{O}_2} + \dot{V}\mathrm{D}\cdot F\mathrm{S}_{\mathrm{O}_2} + \dot{V}\mathrm{AE}\cdot F\mathrm{A}_{\mathrm{O}_2}$$

As $\dot{V}\mathrm{CO}_2$ equals $\dot{V}\mathrm{AE}\cdot F\mathrm{A}_{\mathrm{CO}_2}$, this equation can be rearranged as:

$$F\mathrm{A}_{\mathrm{O}_2} = F\mathrm{S}_{\mathrm{O}_2} - F\mathrm{A}_{\mathrm{CO}_2}\left[F\mathrm{S}_{\mathrm{O}_2} + \frac{\dot{V}\mathrm{F}(F\mathrm{F}_{\mathrm{O}_2} - F\mathrm{S}_{\mathrm{O}_2})}{\dot{V}\mathrm{CO}_2}\right] \quad (2)$$

Whilst this equation may appear somewhat remote from the more usual forms of the alveolar air equation, when $\dot{V}\mathrm{AN}$ is zero it simplifies to:

$$F\mathrm{A}_{\mathrm{O}_2} = F\mathrm{S}_{\mathrm{O}_2} - F\mathrm{A}_{\mathrm{CO}_2}\left[F\mathrm{S}_{\mathrm{O}_2} + \frac{(1 - F\mathrm{S}_{\mathrm{O}_2})}{R}\right]$$

and as $F\mathrm{S}_{\mathrm{O}_2}$ equals inspired oxygen concentration, this expression is in these circumstances identical to the standard alveolar oxygen equation under conditions of inert gas equilibrium.

It will be seen that neither deadspace nor deadspace to tidal volume ratio appear in equation (2). As the gas inspired into the deadspace has the same composition as gas within the system, deadspace merely acts as an extension of the system, and does not influence gas composition within the system.

Selective inspiration of fresh gas

Eger and Ethans (1968) have suggested that certain arrangements of a circle system may behave in a manner very similar to that of a Magill attachment during spontaneous breathing, with fresh gas being selectively disposed towards the alveolar space. For this to occur the system must be able to store fresh gas unmixed with expired gas. If this applies, rebreathing of gas from the system into the alveolar space will not occur when $\dot{V}\mathrm{F}$ equals or exceeds inspired alveolar ventilation values. When fresh gas is less than this value the alveolar inspirate will consist of all fresh gas entering the system, together with some gas previously deposited in the system. Under these circumstances gas in the circle system will have no fresh gas component and will be made up of expired gas which has undergone a volume decrement as a result of carbon dioxide absorption. If the gas in the system has an oxygen concentration $F\mathrm{M}_{\mathrm{O}_2}$, then:

$$(\dot{V}\mathrm{E} - \dot{V}\mathrm{CO}_2)F\mathrm{M}_{\mathrm{O}_2} = \dot{V}\mathrm{AE}\cdot F\mathrm{A}_{\mathrm{O}_2} + \dot{V}\mathrm{D}\cdot F\mathrm{M}_{\mathrm{O}_2}$$

or

$$F\mathrm{M}_{\mathrm{O}_2} = \frac{F\mathrm{A}_{\mathrm{O}_2}}{1 - F\mathrm{A}_{\mathrm{CO}_2}}$$

This must also be the oxygen concentration of vented gas, that is

$$F\mathrm{M}_{\mathrm{O}_2} = F\mathrm{S}_{\mathrm{O}_2}$$

Thus,

$$F\mathrm{A}_{\mathrm{O}_2} = (1 - F\mathrm{A}_{\mathrm{CO}_2})F\mathrm{S}_{\mathrm{O}_2} \quad (\dot{V}\mathrm{AI} > \dot{V}\mathrm{F}) \quad (3)$$

When fresh gas flow equals or exceeds inspired alveolar ventilation, that is when

$$\dot{V}\mathrm{F} \geqslant (\dot{V}\mathrm{AE} + \dot{V}\mathrm{O}_2 - \dot{V}\mathrm{CO}_2 + \dot{V}\mathrm{AN}),$$

and all the alveolar inspirate consists of fresh gas, oxygen uptake will be given by:

$$\dot{V}\mathrm{O}_2 = (\dot{V}\mathrm{AE} + \dot{V}_{\mathrm{O}_2} - \dot{V}\mathrm{CO}_2 + \dot{V}\mathrm{AN})\cdot F\mathrm{F}_{\mathrm{O}_2} - \dot{V}\mathrm{AE}\cdot F\mathrm{A}_{\mathrm{O}_2}$$

and, as $\dot{V}\mathrm{AE} = \dot{V}\mathrm{CO}_2/F\mathrm{A}_{\mathrm{CO}_2}$,

$$F\mathrm{A}_{\mathrm{O}_2} = F\mathrm{F}_{\mathrm{O}_2} - F\mathrm{A}_{\mathrm{CO}_2}\cdot F\mathrm{F}_{\mathrm{O}_2} + \frac{(\dot{V}\mathrm{O}_2(1 - F\mathrm{F}_{\mathrm{O}_2}) - \dot{V}\mathrm{AN}\cdot F\mathrm{F}_{\mathrm{O}_2}}{\dot{V}\mathrm{CO}_2} (\dot{V}\mathrm{F} > \dot{V}\mathrm{AI}) \quad (4)$$

General equation

In each of the above examples the composition of gas within the system is uniform and identical to that of vented gas. This may not always apply. Fresh or expired gas can be selectively vented from or retained within the system. Gas composition within the system may be non-uniform and not equal to that of vented gas.

Gas within a circle system which has passed through the absorber, in inspired gas and in vented gas, can be considered as having two components—a fresh gas component and an alveolar component the composition of which is modified by carbon dioxide absorption. The fresh gas component will have an oxygen concentration of $F\mathrm{F}_{\mathrm{O}_2}$, whilst the alveolar component will have an oxygen concentration equal to $F\mathrm{A}_{\mathrm{O}_2}/(1 - F\mathrm{A}_{\mathrm{CO}_2})$. Deadspace gas which enters the system can also be considered to be made up of these two components. If vented gas is considered to have an alveolar component, $\alpha\dot{V}\mathrm{v}$, and a fresh gas component $(1-\alpha)\dot{V}\mathrm{v}$, then

$$\dot{V}\mathrm{v}\cdot F\mathrm{s}_{\mathrm{O_2}} = \alpha\dot{V}\mathrm{v}\cdot F\mathrm{A}_{\mathrm{O_2}}/(1-F\mathrm{A}_{\mathrm{CO_2}}) + (1-\alpha)\,\dot{V}\mathrm{v}\cdot F\mathrm{F}_{\mathrm{O_2}}$$

or

$$F\mathrm{A}_{\mathrm{O_2}} = (1-F\mathrm{A}_{\mathrm{CO_2}})\cdot\left[\frac{F\mathrm{s}_{\mathrm{O_2}}-(1-\alpha)\,F\mathrm{F}_{\mathrm{O_2}}}{\alpha}\right] \qquad (5)$$

When α is unity, implying that there is no fresh gas component in vented gas, this expression becomes identical to equation (3). The value of α will have a lower limit equal to the absolute value of the expression $(F\mathrm{F}_{\mathrm{O_2}} - F\mathrm{s}_{\mathrm{O_2}})/F\mathrm{F}_{\mathrm{O_2}}$.

Alveolar anaesthetic concentrations

The equations derived above all relate to alveolar oxygen concentration. It is often more useful to have knowledge of alveolar anaesthetic concentrations. If fresh gas contains oxygen and a single anaesthetic agent, then fresh gas anaesthetic concentration will be equal to $(1-F\mathrm{F}_{\mathrm{O_2}})$, and (assuming the anaesthetic agent is the only non-metabolic gas to be considered) anaesthetic concentration in vented gas will equal $(1-F\mathrm{s}_{\mathrm{O_2}})$. Equations for alveolar anaesthetic concentration, $F\mathrm{A}_{\mathrm{AN}}$, can be derived in exactly the same way as for equations (2), (3) and (4) above. A simpler approach, assuming that only three gases are present in the alveolar gas, is to state that:

$$F\mathrm{A}_{\mathrm{AN}} = 1 - F\mathrm{A}_{\mathrm{O_2}} - F\mathrm{A}_{\mathrm{CO_2}}$$

If more than one anaesthetic gas is present or if the contribution of nitrogen is to be taken into account, more complex expressions and greater detail of gas uptake will be needed to calculate $F\mathrm{A}_{\mathrm{AN}}$.

Geometrical representation

The oxygen–carbon dioxide diagram (Rahn and Fenn, 1955) provides a useful method of representing the interrelationships of respired gases. When the co-ordinate oxygen and carbon dioxide points for inspired, expired, end-tidal and alveolar gas are plotted on this diagram (in terms of either partial pressure of fractional concentration) they fall on a straight line, the slope of which is a function of the gas exchange ratio. This is illustrated in figure 2 (left). Conway (1976) similarly showed that, when subjects breathed from a semi-closed anaesthetic system without carbon dioxide absorption, the co-ordinate points for inspired, expired, end-tidal and vented gas all fell on the straight line joining the alveolar and fresh gas points (figure 2 (right)). Such a simple relationship cannot exist during the use of a circle system with carbon dioxide absorption. Under these circumstances fresh and inspired gases will both be carbon dioxide-free, and they will rarely have the same oxygen concentration.

Figure 3 shows a geometrical representation of equation (2), where it is assumed that all fresh and expired gas in the system mix uniformly. Point F represents the co-ordinate point of fresh gas. Inspired gas (point I) has, under total mixing

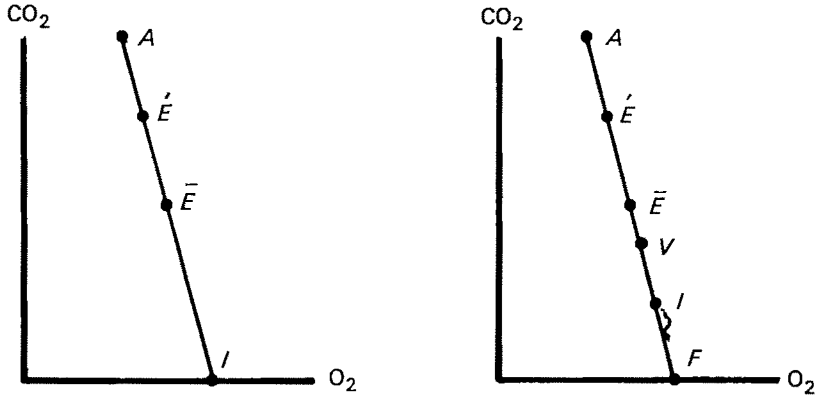

FIG. 2. Left: oxygen–carbon dioxide diagram for a subject breathing air or from a non-rebreathing system. I $\acute{E}$, $\bar{E}$ and A refer to the inspired, mixed expired, end-tidal and alveolar points. Right: oxygen–carbon dioxide diagram for a subject breathing from a rebreathing system without carbon dioxide absorption. The additional points marked F and V refer to fresh and vented gas. Inspired gas may vary in composition, but its co-ordinate point will always lie on the gas exchange line.

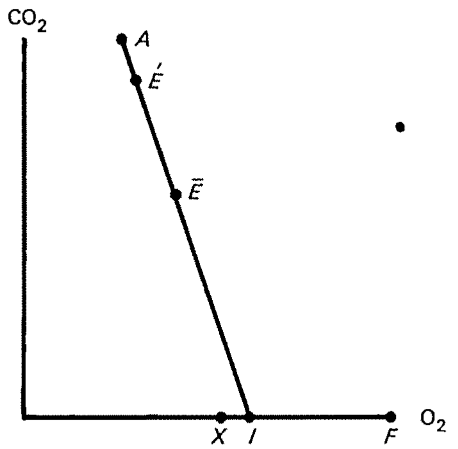

FIG. 3. Oxygen–carbon dioxide diagram for a subject breathing from a circle system in which total mixing of fresh gases occurs. Points F, I, $\bar{E}$ and A refer to fresh, inspired, mixed expired and alveolar gases. Point X represents the oxygen concentration in mixed expired gas after carbon dioxide absorption.

conditions, the same composition as both vented gas ($F\mathrm{s}_{\mathrm{O_2}}$) and the mixture formed in the system. Point A represents alveolar gas. If oxygen and carbon dioxide concentrations are measured continuously at the mouth, then the tidal point plotted on this diagram will remain at point I during inspiration, and rise along the line joining points I and A during expiration, to end at the end-tidal point, $\acute{E}$. Mixed expired gas will have a co-ordinate point ($\bar{E}$) which also lies on this straight line. After entry into the circle system, carbon dioxide will be removed from expired gas. This gas will undergo a volume reduction and its oxygen concentration will increase. Point X represents the co-ordinate point of mixed expired gas after carbon dioxide absorption. Mixing of this gas with fresh gas will result in the formation of a mixture the co-ordinate point of which lies again at point I.

Figure 4 is a quantitative representation of equation (2) at various values of anaesthetic gas uptake. In this diagram fractional oxygen and carbon dioxide concentrations in respired gases are plotted for a subject breathing from a circle system in which total gas mixing is present. Fresh gas consists of 50% nitrous oxide in oxygen supplied at a flow of 1000 ml min^{-1} ATPD. Oxygen uptake and carbon dioxide output are assumed to have constant values of 200 and 160 ml min^{-1} STPD respectively. At this carbon dioxide output and with no carbon dioxide in inspired gas, an $F\mathrm{A}_{\mathrm{CO_2}}$ of 0.05 will result if alveolar ventilation is 3200 ml min^{-1} STPD (3870 ml min^{-1} BTPS). The lines on figure 4 represent "gas exchange" lines at nitrous oxide uptake values varying from zero to 400 ml min^{-1} STPD. The intersection of each line with the baseline represents $F\mathrm{I}_{\mathrm{O_2}}$, equal to $F\mathrm{s}_{\mathrm{O_2}}$ at each nitrous oxide uptake. The two points on each line

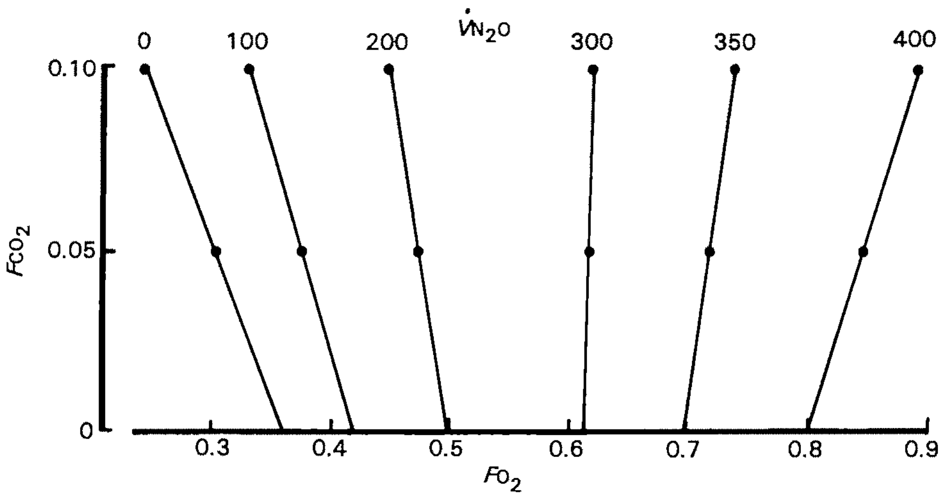

FIG. 4. The effects of variations in anaesthetic uptake on the oxygen–carbon dioxide diagram during use of the circle system. Fresh gas is 50% nitrous oxide in oxygen supplied at a flow of 1000 ml min^{-1} ATPD. Total mixing in the system is assumed. $\dot{V}\mathrm{O_2}$ and $\dot{V}\mathrm{CO_2}$ have values of 200 and 160 ml min^{-1} STPD respectively. The lines represent gas exchange lines at varying values of nitrous oxide uptake ($\dot{V}\mathrm{N_2O}$) expressed at STPD. The two points marked on each line are alveolar points at $F\mathrm{A}_{\mathrm{CO_2}}$ 0.05 and 0.10.

represent alveolar points at $F\text{A}_{CO_2}$ values of 0.05 and 0.10. The alveolar points corresponding to higher values of $F\text{A}_{CO_2}$ will lie on extensions of these lines.

Figure 4 illustrates the effect of variations of anaesthetic uptake on both the position and slope of the "gas exchange" lines. As nitrous oxide increases from zero towards a value equal to that of oxygen uptake, so $F\text{I}_{O_2}$ (equal to $F\text{S}_{O_2}$) increases from an initial low value eventually to equal the fresh gas oxygen value of 0.5. When nitrous oxide uptake exceeds oxygen uptake, $F\text{S}_{O_2}$ and $F\text{I}_{O_2}$ exceed $F\text{F}_{O_2}$. As nitrous oxide uptake increases, so the gas exchange lines become steeper. At a nitrous oxide uptake close to 300 ml min^{-1} (in fact, 291.3 ml min^{-1}) the "gas exchange" line becomes vertical, implying that under these conditions $F\text{A}_{O_2}$ is ventilation-independent. Greater nitrous oxide uptake results in "gas exchange" lines with positive slopes. Under these circumstances as ventilation decreases and $F\text{A}_{CO_2}$ increases, so $F\text{A}_{O_2}$ will also increase. Such a paradoxical relationship between $F\text{A}_{CO_2}$ and $F\text{A}_{O_2}$ at high values of nitrous oxide uptake was predicted by Farhi and Olszowska (1968), who indeed suggested that under conditions of high inert gas uptake ventilation–perfusion mismatch in the lungs could result in negative alveolar–arterial oxygen gradients. The right-hand side of figure 4 thus illustrates an extreme example of the effects of uptake of one component of inspired gas on alveolar concentrations of other components.

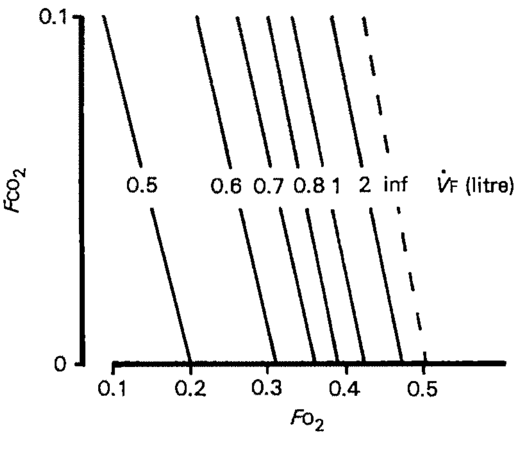

FIG. 5. The effects of variations in fresh gas flow on the oxygen–carbon dioxide diagram. Total mixing is assumed. The conditions of use are: $\dot V\text{O}_2 = 200\,\text{ml min}^{-1}$, $\dot V\text{CO}_2 = 160\,\text{ml min}^{-1}$, $\dot V\text{N}_2\text{O} = 100\,\text{ml min}^{-1}$ (all at STPD), $F\text{F}_{O_2} = 0.50$. The interrupted line refers to an infinitely high fresh gas flow and is calculated from equation (4), whilst for the other lines $\dot V\text{F}$ is expressed at ATPD and the slope and position have been calculated from equation (2).

The slopes and positions of the lines shown in figure 2 are a function of gas uptake and inspired (or fresh) gas composition. These factors influence the slopes and positions of the lines shown in figure 4, but additionally, the characteristics of these lines are influenced by fresh gas flow. Figure 5 shows the effects on these lines of varying fresh gas flow to a circle system in which total gas mixing is present. Oxygen and anaesthetic uptake and carbon dioxide output here have constant values of 200, 100 and 160 ml min^{-1} STPD and fresh gas consists of 50% nitrous oxide in oxygen. The dotted line at the right-hand side of this diagram represents gas exchange relationships that would apply under these circumstances if fresh gas flow were infinitely high, equivalent to the subject being attached to a non-rebreathing system. As fresh gas flow is reduced towards basal values the "gas exchange" lines are shifted to the left of the oxygen–carbon dioxide diagram. They also change in slope, although these changes are less marked than the alterations in slope related to changing nitrous oxide uptake.

Figures 3–5 are oxygen–carbon dioxide representations of equation (2) and relate to a state of total gas mixing in a circle system. Equation (3), based on an assumed selective inspiration of fresh gas, can be considered as representing a non-mixing state. Whilst such a form of gas disposition may represent a remote form of circle system behaviour, it is useful to compare the implications of this state with those of total mixing. In figure 6 the interrupted line on the oxygen–carbon dioxide diagram represents the gas exchange state when total mixing is present, whilst the continuous line shows behaviour in the non-mixing state. In both cases fresh gas flow is 1000 ml min^{-1} ATPD, fresh gas contains 50% nitrous oxide in oxygen, whilst oxygen uptake, carbon dioxide output and nitrous oxide uptake are 200, 160 and 150 ml min^{-1} STPD respectively. Point F on this diagram represents the oxygen concentration in fresh gas. Point S is the value for $F\text{S}_{O_2}$ as defined in equation (1), and the baseline intercepts of both lines lie at this point. If total mixing of fresh and expired gas is present the alveolar point will lie on the line SZ.

Equation (3) only applies to a non-mixing state if inspired alveolar ventilation exceeds fresh gas flow. If this is not so, then all the alveolar inspirate will consist of fresh gas and gas exchange will not be influenced by the behaviour of the circle system. The line joining points S and X on figure 6 represents the situation when alveolar inspiratory ventilation exceeds fresh gas flow and equation (3) applies. Under these circumstances the alveolar point will lie on this line, its position being determined by the value of $F\text{A}_{\text{CO}_2}$. As ventilation decreases a point will be reached when fresh gas flow exactly satisfies alveolar inspiratory requirement. Under the defined circumstances of gas exchange and fresh gas flow, this is shown at point X on figure 6. Further reductions in alveolar ventilation will result in an alveolar point lying on the line XY, the baseline intercept of which is at point F. When the alveolar point lies on segment SX of the gas exchange line, gas sampled at the mouth during inspiration will not necessarily have a uniform composition. The state of gas disposition implied for equation (3) implies that the first portion of inspired gas will be fresh gas, later followed by gas from the circle system. During inspiration the co-ordinate point will initially lie at point F and at some time in inspiration move to point S. During expiration the tidal point will rise along line SX. When fresh gas flow just satisfies inspired alveolar requirements the co-ordinate point during inspiration will lie at point F until alveolar filling is complete, and then move to point S as the deadspace fills with gas from the circle system. A further reduction in ventilation (or an increase in fresh gas flow) will lead to gas in the system and vented from it ceasing to be equivalent to alveolar gas from which carbon dioxide has been removed and becoming a mixture of fresh gas and carbon dioxide-free alveolar gas, the co-ordinate point of which will lie between points F and S on figure 6.

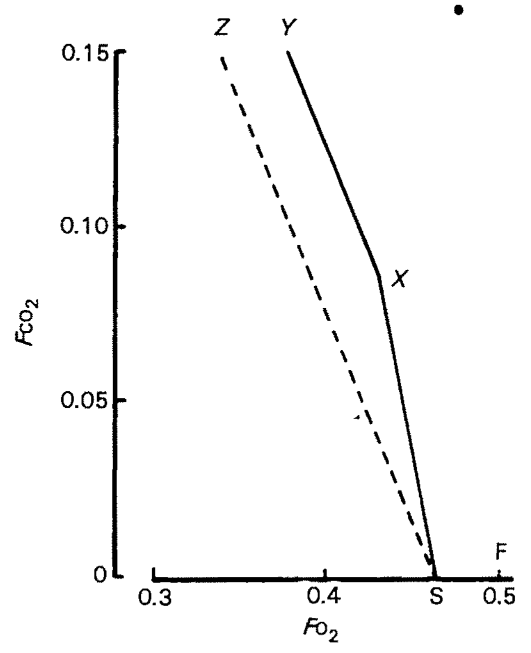

FIG. 6. Selective inspiration of fresh gas. In this oxygen–carbon dioxide diagram $\dot{V}\text{O}_2 = 200\,\text{ml min}^{-1}$, $\dot{V}\text{CO}_2 = 160\,\text{ml min}^{-1}$, $\dot{V}\text{N}_2\text{O} = 150\,\text{ml min}^{-1}$ (all at STPD), $\dot{V}\text{F} = 1000\,\text{ml min}^{-1}$ ATPD, $F\text{F}_{\text{O}_2} = 0.50$. Point F refers to fresh gas and point S relates to $F\text{S}_{\text{O}_2}$ as defined in the text. Line SZ is the gas exchange line from equation (2) for total gas mixing, whilst line SXY relates to selective inspiration of fresh gas and relates to equations (3) and (4).

Graphical representations of alveolar gas relationships

As has been pointed out above, equation (3) of this paper represents an unlikely form of behaviour of a circle system. Whilst equation (5) has a general application, many factors will influence the value of the term α. As a simplification for purposes of graphical representation, it will here be assumed that total mixing of fresh and expired gas entering a circle system occurs, and that equation (2) above applies. As fresh gas flow to a circle system becomes small in relation to both ventilation values and the volume of the system, a tendency to a total mixing state is more likely to be present.

Figure 7 shows values of $F\text{A}_{\text{O}_2}$, based on equation (2), for constant values of fresh gas composition, ventilation and metabolic gas exchange and at varying values of fresh gas flow and anaesthetic uptake. Fresh gas is here assumed to be 50% nitrous oxide in oxygen. Alveolar oxygen concentrations are greater than fresh gas oxygen values when anaesthetic uptake is high. As fresh gas flow is reduced from high to low values so $F\text{A}_{\text{O}_2}$ tends to change, increasing when anaesthetic uptake is high and decreasing when it is low. These changes are slight at high values of fresh gas flow but become increasingly marked as fresh gas flow approaches minimal limiting values. When anaesthetic and oxygen uptakes are equal $F\text{A}_{\text{O}_2}$ is here independent of fresh gas flow. Under any conditions of fresh gas composition this state occurs when $\dot{V}\text{AN}/\dot{V}\text{O}_2 = (1 - F\text{F}_{\text{O}_2})/F\text{F}_{\text{O}_2}$. When this relationship does not apply, $F\text{A}_{\text{O}_2}$ will tend

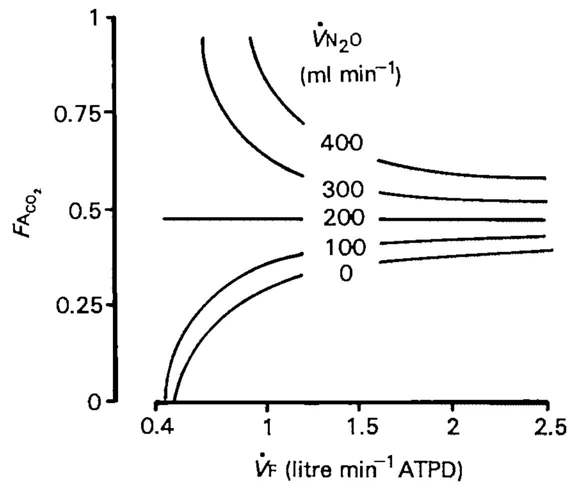

FIG. 7. The relationships between alveolar oxygen concentrations and fresh gas flow during use of a circle system with nitrous oxide. Fresh gas consists of 50% nitrous oxide in oxygen, $\dot{V}O_2 = 200$ ml min^{-1}, $\dot{V}CO_2 = 160$ ml min^{-1} (both at STPD) and $FA_{CO_2} = 0.05$. Total gas mixing is assumed. The five lines relate FA_{O_2} to $\dot{V}F$ at different values of nitrous oxide uptake (expressed at STPD).

either to zero or to $(1 - FA_{CO_2})$ as fresh gas flow is reduced. As it is here assumed that dry alveolar gas is made up only of oxygen, carbon dioxide and anaesthetic, a high FA_{O_2} implies a low alveolar anaesthetic concentration.

Figure 7 shows that at low values of fresh gas flow and anaesthetic uptake, dangerously low FA_{O_2} values may occur when nitrous oxide is administered. Circle systems are commonly used to administer potent inhalation agents with high concentrations of oxygen. Under these circumstances unduly low FA_{O_2} values are a remote (although still possible) result of low fresh gas flows and anaesthetic uptake. The minimum FA_{O_2} that can exist will be equal to $(1 - FA_{CO_2} - F_{sat})$, where F_{sat} is the saturated vapour fractional concentration of the agent at body temperature. With the exception of diethyl ether, volatile liquid anaesthetics in common use do not have F_{sat} values great enough to make this limiting value dangerously low. Marked changes in alveolar anaesthetic concentrations can still occur when fresh gas flow and anaesthetic uptake change. Figure 8 shows calculated alveolar halothane concentrations at varying values of fresh gas flow and halothane uptake. As fresh gas flow decreases, alveolar halothane will tend to zero when halothane uptake is high and may reach unduly high values at low values of halothane uptake.

Buffering effects of circle system

The equations derived above defining the composition of gas vented from and within a circle

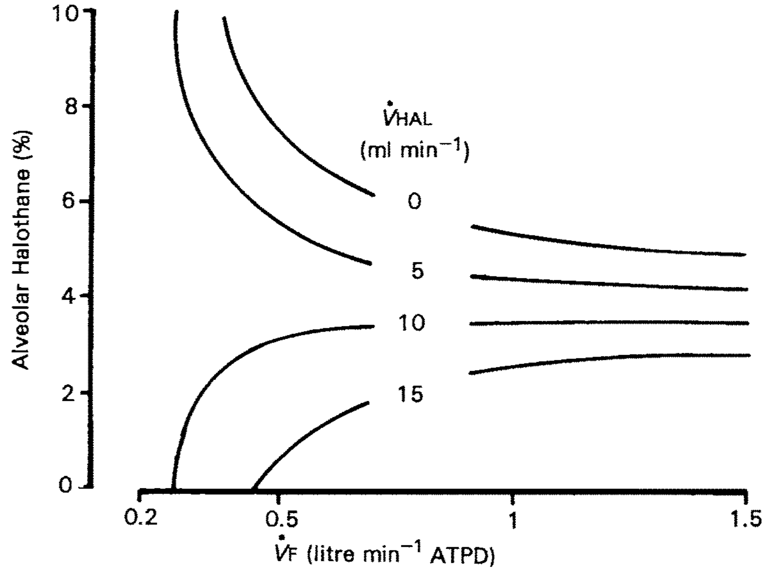

FIG. 8. Alveolar halothane concentrations and fresh gas flow during use of a circle system. Fresh gas consists of 4% halothane in oxygen. Total gas mixing is present. $\dot{V}O_2 = 200$ ml min^{-1} STPD, $\dot{V}CO_2 = 160$ ml min^{-1} STPD, $FA_{CO_2} = 0.05$. Alveolar halothane percentage is shown for varying values of fresh gas flow at four values of halothane uptake (expressed at STPD).

system and of alveolar gas all relate to equilibrium states. If any of the variables affecting alveolar and circle system gas composition change then alveolar and system gas composition will take a finite time to reach a new equilibrium. The volume of a circle system plays an important role in determining the time taken for such changes to occur.

Because of the cyclical nature of ventilation, gas exchange within the circle–subject complex is discontinuous. If it is assumed that gas exchange is a continuous phenomenon (equivalent to assuming an infinite respiratory frequency) the rate of attainment of an equilibrium state can be defined by a simple exponential expression. Figure 9 shows calculated changes of gas composition in a circle system with total gas mixing, initially in equilibrium and following an increase in fresh gas flow when respiratory frequency has values of 1 and 10 min^{-1} and when it is infinitely high. Gas uptake and ventilation have been assumed to be constant and total gas mixing is assumed to be present. The two lines representing the low respiratory frequencies pass through the end-expiratory concentrations of gas in the system, equivalent to $F\text{s}_{O_2}$. The lines representing an infinite respiratory frequency and one of 10 b.p.m. nearly coincide. If the same calculations are made for a decrease rather than an increase of fresh gas flow, these two lines would be superimposed on this graph scale. Thus negligible errors result from assuming that a change towards a new equilibrium state will follow an exponential time-course. If the initial concentration of any component, C, within the system is defined as C_0, and the final concentration at equilibrium is defined as C_f, the concentration at time t, C_t, is given by

$$C_t = C_f - (C_f - C_0)e^{-t/\Upsilon}$$

The time constant Υ is given by:

$$\Upsilon = \frac{V\text{s}}{\dot{V}\text{F} - \dot{V}\text{O}_2 - \dot{V}\text{AN}}$$

where $V\text{s}$ is the volume of the circle system. Thus the time constant will be short when system volume is small or fresh gas flow high. As fresh gas flow tends towards the sum of oxygen and anaesthetic uptakes, so Υ tends to infinity. For given values of system volume and gas uptakes the relationships between fresh gas flow and Υ are shown in figure 10. This time constant does not take account of rates of changes in composition of gases within the subject's functional residual capacity.

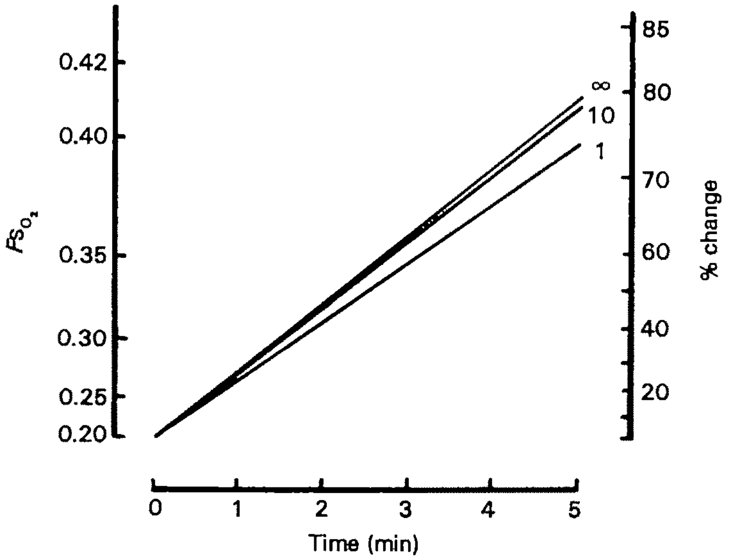

FIG. 9. Calculated rates of change of gas vented from a circle system ($F\text{s}_{O_2}$) following a sudden change in fresh gas flow. At equilibrium the change in $\dot{V}\text{F}$ should alter $F\text{s}_{O_2}$ from 0.20 to 0.47. The lines marked 1 and 10 join the calculated end-expiratory $F\text{s}_{O_2}$ values at these two respiratory rates, whilst for the line marked ∞ gas exchange has been assumed to be a continuous phenomenon. System volume 5000 ml; $\dot{V}\text{F}$ increased from 500 to 2000 ml min^{-1}. Time constant = 3.2 min.

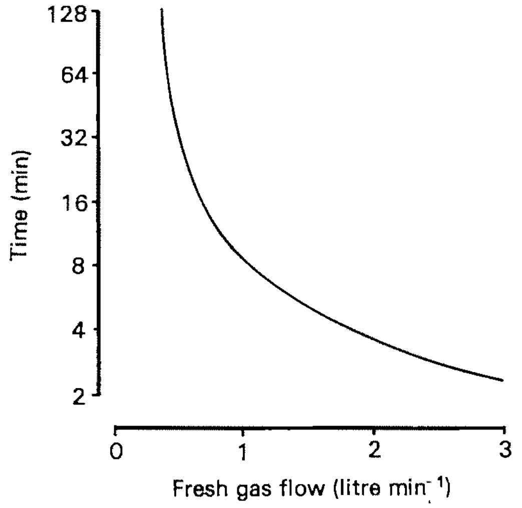

FIG. 10. The time constant of change of a circle system and fresh gas flow. System volume = 6000 ml; oxygen uptake = 200 ml mm^{-1}; nitrous oxide uptake = 100 ml min^{-1}.

Totally closed systems

If oxygen and anaesthetic gas are supplied in fresh gas at a rate equal to their uptake, no gas is vented from the system. As the expression $F\mathrm{s}_{O_2}$ is now meaningless, all of the alveolar gas equations described above become invalid. Under these circumstances gas composition within the system should be constant as all the components of fresh gas are removed by the subject. In theory, if fresh gas flow is reduced abruptly from greater than basal values to one which in both flow and composition exactly satisfies gas uptake, alveolar gas composition should remain unchanged from its state before the reduction. In practice, it is unlikely that such an exact balance between fresh gas composition and gas uptake could be achieved or maintained. If the system volume remains constant at a value $V\mathrm{s}$ and the sum of oxygen and anaesthetic gas uptakes is numerically equal to fresh gas flow, then oxygen concentration within the system after time t, C_t, will be related to the initial oxygen concentration, C_0, by the expression:

$$C_t = C_0 + \frac{(\dot{V}\mathrm{F} \cdot F\mathrm{F}_{O_2} - \dot{V}_{O_2})t}{\dot{V}\mathrm{s}}$$

If the oxygen supplied in fresh gas differs but slightly from oxygen uptake, the last term on the right of this equation will be small and C_t will change very slowly.

DISCUSSION

Several simplifying assumptions have been in the derivation of the various expressions defined in the foregoing analyses. The limitations imposed by these assumptions affect the accuracy and applicability of the various equations. These expressions should be regarded as being able to give a guide to the behaviour of circle systems rather than as tools for the accurate calculation of alveolar gas composition under any given conditions of use.

An obvious limitation of the analyses concerns their dependence on the degree of mixing of fresh and expired gas in the system. Equation (2) and (3) relate to the presence of total gas mixing and selective inspiration of fresh gas respectively. In practice, an unpredictable degree of gas mixing is likely to be present. Eger and Ethans (1968) have shown that gas disposition within a circle system is related to the geometry of the system. Whilst some arrangements of circle components will result in the selective venting of expired gas from the system, other arrangements may lead to fresh gas being lost and expired gas retained. In another context, Schoonbee and Conway (1981) showed that, with any given circle arrangement and values of fresh gas flow and ventilation, gas mixing in the system was considerably influenced by changes in respiratory frequency. Whilst alveolar gas equations related to equations (2) and (3) can be deduced from any given forms of gas disposition, these have little practical value. Equation (5), which is a general equation to describe circle behaviour, does not avoid the problem for the value of the term α of this equation is an implicit function of gas disposition within the system. In deriving the figures which illustrate the relationships between fresh gas flow and alveolar oxygen and anaesthetic concentration, a state of total gas mixing has been assumed to be present. Total gas mixing is more likely to occur when fresh gas flow is low in relation to system volume and ventilation, when fresh gas enters the system on the absorber side of the unidirectional valves, and when respiratory frequency is high.

A more severe restriction on the validity of these expressions relates to the assumption of an equilibrium state between the subject and circle system. Equation (1) assumes that oxygen uptake by the subject will always be equal to the difference in the amounts of oxygen contained in fresh and vented gases. If gas composition within the system is changing this need not apply. The difference may now relate not only to oxygen uptake by the subject, but also to retention or loss of oxygen from the system itself. If the mean volume of the system is constant, cumbersome expressions can be derived to correct for this error. The magnitude of the error will depend upon the rate of change of gas composition within the system and thus be inversely related to the time constant of change.

A major restriction of the validity of this analysis is related to the constant values for anaesthetic uptake that have been assumed in all of the equations derived in this paper. In practice, anaesthetic uptake will vary with time throughout the course of an anaesthetic, decreasing at a rapid rate early in administration and still changing at a slow rate after several hours of administration. Furthermore, anaesthetic uptake by the subject will be a function of inspired anaesthetic concentration. This particular aspect of a circle system behaviour has not been considered in the present analyses. The relationship of anaesthetic uptake to inspired anaesthetic concentration and therefore to gas composition within a circle system can be considered as a further buffering effect of a circle system at low fresh gas flows. At high anaesthetic uptake and low fresh gas flows, anaesthetic concentration in the system will tend to decrease and this decrease will limit uptake.

Appreciable volumes of nitrogen will be present in the subject at the start of administration, and excretion of this nitrogen into the circle system may greatly affect behaviour of the system. The nitrogen stores of an adult subject are in the order of 3 litre, of which some two-thirds are contained in the lung and the remainder is fairly equally divided between body water and body fat. If a low fresh gas flow is used from the start of administration, excretion of nitrogen into the system will severely dilute all other gases present. Most of the nitrogen present in the lungs and body water can be removed by breathing a nitrogen-free gas for about 20 min. Nitrogen from body fat will be slowly excreted over several hours. Barton and Nunn (1975) found, in subjects initially given a 10-min period of denitrogenation and then attached to a circle system to which basal gas flows were supplied, that mean nitrogen concentrations within the system reached 10% after 1 h.

The lack of an equilibrium state also affects the accuracy of the expressions above which describe the buffering effects of circle systems. If anaesthetic uptake is changing, so is the time-constant of the system and the course of change will also vary. The influence of changing anaesthetic uptake on this time constant will be pronounced in the early stages of administration and will have a decreasing influence with time as the rate of change of uptake decreases.

Whilst the various equations defined in this paper cannot be used to predict with accuracy alveolar gas concentrations under any stated conditions of use of a circle system, they do give good indications of the manner of function of such a system and the directions of influence of the variables which affect its performance. They can also give guidance to the manner in which a circle system is used. There are two good reasons, when using a circle system, to use high flows of fresh gas for the first 20 min or so of administration. At the start of anaesthetic administration, anaesthetic uptake will be at a maximum and the equilibrium of the system potentially at its least stable. The effects of disequilibrium on the subject are minimized by the use of high fresh gas flows. An initial period with a high fresh gas flow will result in the majority of nitrogen in the subject's functional residual capacity and well perfused body tissues being eliminated. Thereafter it is likely that the greatest stability will occur if fresh gas flow is reduced abruptly to close to predicted basal values. The long time-constant of a circle system at such low flows will result in any changes in alveolar gas composition resulting from mismatching between fresh gas composition and gas uptake occurring very slowly. As neither the ability to calculate gas uptake nor the buffering effects of a circle system can be fully relied upon, it would seem mandatory when low flows are used to monitor the composition of gas within (or emerging from) a circle system.

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RELATIONS DU GAZ ALVEOLAIRE PENDANT L'USAGE D'UN SYSTEME EN CIRCUIT FERME AVEC ABSORPTION DE GAZ CARBONIQUE

RESUME

Des expressions ont été dérivées pour montrer la dépendance de l'oxygène alvéolaire et des concentrations anesthésiantes sur le débit de gaz frais allant à un système en circuit fermé, la composition de gaz frais, la ventilation et la fixation du gaz. La forme de ces expressions est influencée par le degré de mixage des gaz frais et des gaz expirés à l'intérieur du système en circuit fermé. Ces expressions supposent un état d'équilibre à l'intérieur de ce système et le taux auquel on s'approchera de l'équilibre a été quantifié en termes de constantes de temps du changement de la composition du gaz à l'intérieur du système. Les constantes de temps s'approchent de l'infini au fur et à mesure que le débit de gaz s'approche des valeurs qui satisfont à la fixation du gaz. Bien que cela simplifie les suppositions qui ont été faites dans la dérivation des divers gaz alvéolaires, les équations limitent leur précision; mais l'expression peut servir de guide en ce qui concerne le comportement possible des systèmes en circuit fermé, quelles que soient les conditions d'utilisation.

ALVEOLÄR-GASZUSAMMENHÄNGE WÄHREND VERWENDUNG DES KREISSYSTEMS MIT KOHLENDIOXYDABSORPTION

ZUSAMMENFASSUNG

Expressionen wurden abgeleitet, um die Abhängigkeit von alveolärem Sauerstoff und narkotischen Konzentrationen vom Frischgasfluss in ein Kreissystem, von der Zusammensetzung des Frischgases, der Belüftung und des Gasaufnahme zu zeigen. Die Form dieser Expressionen ist vom Mischungsausmass frischer und ausgeatmeter Gase innerhalb des Kreissystems beeinflusst. Diese Expressionen erreichen im Kreissystem einen Gleichgewichtszustand, und das Tempo, mit dem dieser erreicht wird, wurde durch die Zeitkonstanten ausgerdrückt, die die Änderungen der Gasmischung innerhalb des Systems bestimmen. Die Zeitkonstanten nähern sich der Unendlichkeit, sobald der Frischgaszufluss Werte erreicht, die gerade der Gasaufnahm entsprechen. Obwohl vereinfachende Annahmen bezüglich der Ableitung der verschiedenen Alveolärgasgleichungen deren Genauigkeit beschränken, kann die Expression als Richtlinie für das wahrscheinliche Verhalten von Kreissystemen unter jeweils gegebenen Bedingungen dienen.

RELACIONES DEL GAS ALVEOLAR DURANTE EL USO DEL SISTEMA CIRCULAR CON ABSORCION DE DIOXIDO DE CARBONO

SUMARIO

Se han elaborado expresiones para mostrar la dependencia de las concentraciones de gas anestésico y de óxigeno alveolar con respecto a un flujo de gas puro en un sistema circular, a la composición del gas puro, a la ventilación y a la respiración del gas. La configuración de estas expresiones viene influenciada por el grado de la mezcla de gases puros y expirados dentro del marco del sistema circular. Estas expresiones asumen un estado de equilibrio dentro del sistema circular y el régimen de acercamiento a este estado de equilibrio se ha cuantificado en términos de las constantes de tiempo del cambio de composición del gas dentro del sistema. Las constantes de tiempo tienden a infinito a medida que el flujo de gas puro se acerca a los valores que satisfacen en la justa medida la absorción de gas. Aunque las asunciones tendentes a la simplificación, efectuadas en la derivación de las diversas ecuaciones del gas alveolar, limitan su precisión, la expresión puede sevir como guia para la posible conducta del sistema circular bajo cualquier condición dada de uso.

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EFFECT OF ORAL DIAZEPAM ON LOWER OESOPHAGEAL SPHINCTER PRESSURE

B. R. Cotton, G. Smith and D. Fell

SUMMARY

The effect of diazepam 10 mg orally was investigated on lower oesophageal sphincter pressure in a random double-blind study of nine healthy volunteers. Barrier pressure decreased to a small but statistically significant extent. The reduction in barrier pressure was not related to the level of drowsiness.

The tendency to regurgitate is related to the barrier pressure (BP) which is the difference in pressure between gastric (GP) and the lower oesophageal sphincter (LOS) or high pressure zone (HPZ). Any drug which decreases BP may increase the risk of reflux from stomach to the oesophagus.

In an uncontrolled study in humans and monkeys diazepam decreased BP and increased gastro–oesophageal reflux as indicated by oesophageal pH testing (Hall et al., 1975). Only a single measurement at an unspecified time interval was made following the i.v. injection of diazepam 2.5–10 mg. In a double-blind study diazepam 5 or 10 mg i.v. in healthy volunteers had no effect on BP, but 20 mg produced a significant increase in BP (Weiruch et al., 1979); measurements were made at 10-min intervals for 2 h. In view of these conflicting data we have undertaken a study of the effects of oral diazepam on LOS in healthy volunteers.

METHODS

Informed consent to this study was obtained from nine healthy volunteers (ages 23–29 yr) with no history of gastrointestinal, respiratory or cardiovascular disease, and not receiving any drug therapy. Four subjects were male and five female, and none was a tobacco smoker. All subjects had fasted for at least 6 h before the study.

Each volunteer attended on two occasions, separated by at least 1 week. After a control sample of venous blood had been taken from the antecubital fossa for measurement of plasma diazepam concentration, the subject swallowed either diazepam 10 mg contained in two capsules or two identical capsules containing an inert placebo. The pairs of capsules were distributed in a double-blind random manner.

Thirty minutes later the subject swallowed a silastic nasogastric tube (3 mm o.d.) into which were embedded three subminiature strain gauge pressure transducers at 5, 10 and 15 cm from the distal tip (Gaeltec Ltd). This was connected via a pre-amplifier to a chart recorder (Linearcorder Mk III). Each transducer was calibrated by immersion in a column of water at 37 °C. The tube was swallowed until all the transducers were in the stomach and a period of 15 min allowed to elapse to enable gastric motility to settle.

Measurements of gastric (GP) and high pressure zone (HPZ) pressures were made by withdrawal of the tube from the stomach, 0.5 cm at a time with pauses for a few seconds, through the HPZ until all the transducers were in the oesophagus. Pressure changes produced by swallowing were evident on the oesophageal trace and recognized as described previously (Smith, Dalling and Williams, 1978). Our techniques have been described in detail previously (Cotton and Smith, 1981).

Measurements were commenced 45 min after ingestion of the capsules and at 5-min intervals for a further 30 min. Each volunteer acted as his or her own control. At the end of recording, the tube was removed and the zero baseline and calibration reassessed. On all occasions zero drift and changes in calibration were minimal. A further sample of venous blood was then taken for measurement of plasma diazepam concentration. During the course of the study, the investigator (unaware of

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the nature of the contents of capsules) graded the condition of the subject as follows:

− = awake and alert
+ = slightly drowsy
+ + = definitely drowsy
+ + + = asleep but easily rousable
+ + + + = asleep but barely rousable

All results were subjected to analysis of variance with replications and also by Student's *t* test.

Plasma concentrations of diazepam were measured by high performance liquid chromatography following benzene extraction according to the technique of Cotler, Puglisi and Gustafson (1981), modified slightly by using saturated potassium chloride solution as the carrier vehicle.

RESULTS

Figure 1 shows that the barrier pressure was reduced slightly following the administration of diazepam and that this decrease persisted for 30 min until the end of recording. Unpaired Student's *t* test applied to values at various sample times revealed a significant difference ($P < 0.05$) between placebo and diazepam only at 50 min following administration.

A two-way analysis of variance with replications revealed an overall significant difference in barrier pressure between placebo and diazepam ($P < 0.01$) with no significant effect attributable to elapsed time following either drug or placebo.

Table I shows the individual results, drowsiness scores and plasma diazepam concentrations. There is no correlation between plasma diazepam concentration and the mean decrease of barrier pressure ($r = 0.07$) or the drowsiness score ($r = 0.35$). In addition, there is no correlation

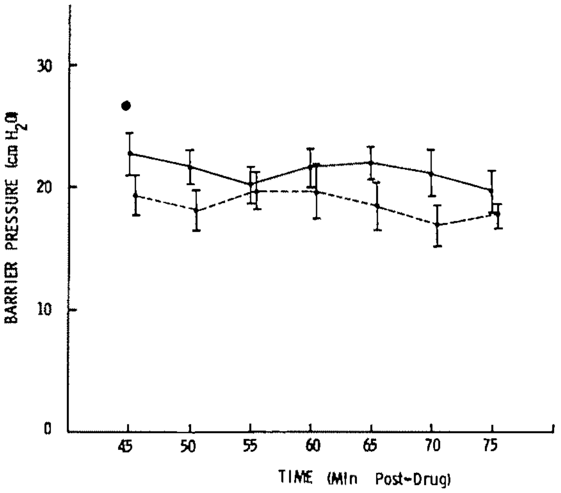

FIG. 1. Effect of oral diazepam 10 mg (---) and placebo (——) on barrier pressure in nine subjects.

TABLE I. *Individual results, drowsiness scores and plasma diazepam concentrations*

Subject	Wt (kg)	Drug	Barrier pressure (cm H_2O) at times (min) after drug							Plasma concn diazepam (ng ml^{-1})	Drowsiness score
			45	50	55	60	65	70	75		
1	78	Placebo	29	22.5	21.5	23	21.5	13	11.5	0	−
		Diazepam	16	17	17.5	20.5	13	15	15.5	138	+ +
2	74	Placebo	18	21	16	15.5	25	30	21.5	0	−
		Diazepam	20	16	20	20	19	21.5	19.5	90	+
3	78	Placebo	20.5	19	20	20	20	15	19.5	0	−
		Diazepam	13.5	16.5	18	23	24	22	16	140	+
4	58	Placebo	24.5	27.5	14	16	21	15.5	13.5	0	−
		Diazepam	21.5	17.5	18.5	12	10	17.5	16	114	+ +
5	54	Placebo	21	17.5	20	20	20.5	15.5	18.5	0	−
		Diazepam	23	28	31	35.5	29	19	21	288	+ +
6	54	Placebo	12.5	17	15.5	29	17	21	17	0	−
		Diazepam	15.5	17.5	16.5	18.5	13.5	8	19.5	230	+ +
7	57	Placebo	28.5	25.5	25.5	22.5	29.5	29.5	30	0	−
		Diazepam	27	21.5	20	20.5	21	21.5	22.5	148	+ + + +
8	65	Placebo	24	23	24.5	20.5	24	27.5	25	0	−
		Diazepam	16	16.5	19	14.5	21	15.5	17	190	+
9	50	Placebo	27	22	24.5	28.5	20	22.5	21	0	−
		Diazepam	21.5	12	17.5	13	15.5	12	13.5	388	+ + +

between barrier pressure and drowsiness score ($r = 0.28$).

DISCUSSION

Our results show that diazepam exerts an effect on LOS to decrease barrier pressure. We have shown also that this effect may persist for up to 1 h following administration, but there is considerable variation in this action during such a period of time.

Diazepam 10 mg orally is in the dose range used for anaesthetic premedication. Peak plasma concentrations occur at about 60 min following ingestion, and a decrease in plasma concentrations occurs after about 90 min (Gamble, Dundee and Assaf, 1975). Our measurements were made at 45–75 min after ingestion and should have encompassed the period of peak plasma concentrations.

The central mechanisms of action of diazepam are obscure and at the moment there are two main theories. The first suggests that the sedative and anticonvulsant effects of diazepam are related to an enhanced inhibitory neurotransmission mediated by gamma-aminobutyric acid (GABA) (Costa and Guidotti, 1979). The second states that the muscle relaxation and anti-anxiety properties produced by diazepam results from an enhanced inhibitory neurotransmission mediated by glycine (Snyder, Enna and Young, 1977). Both theories involve central actions; there is no evidence for either glycine or GABA receptors in the region of the LOS.

There was marked individual variation in response to diazepam in respect of drowsiness and effect on LOS. This variation was not related to plasma concentrations and this is in agreement with previous findings with regard to sedation (Mandelli, Tognoni and Garattini, 1978).

We do not feel confident in recommending oral diazepam in this dosage as a safe premedicant with regard to lack of risk of regurgitation. Although one subject (table I, No. 5) exhibited an increase in barrier pressure, those subjects with the highest drowsiness score (Nos 7 and 9) had the greatest decreases in BP, but there was considerable variation in response among our subjects. The difficulty in predicting responses to diazepam in individuals both in terms of development of drowsiness and decrease in LOS pressure suggests that care must be exercised in the use of this drug. Some patients may exhibit a considerable decrease in BP and suffer increased risk of regurgitation.

ACKNOWLEDGEMENTS

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EFFET DU DIAZEPAM ADMINISTRE PAR VOIE BUCCALE SUR LA PRESSION EXERCEE SUR LE SPHINCTER OESOPHAGIEN INFERIEUR

RESUME

L'effet de 10 mg de diazépam administré par voie buccale, sur la pression excercée sur le sphincter oesophagien a fait l'objet de recherches au cours d'une étude à double inconnue effectuée au hasard sur neuf volontaires en bonne santé. La pression sur la barrière a diminué dans une petite mesure qui a toutefois eu une importance statistique significative. La réduction de la pression sur la barrière n'a pas été liée au niveau de somnolence.

DIE AUSWIRKUNG DER PERORALEN VERABREICHUNG VON DIAZEPAM AUF DEN NIEDEREN SPEISERÖHRENSCHLIESSMUSKELDRUCK

ZUSAMMENFASSUNG

Die Auswirkung der peroralen Verabreichung von 10 mg Diazepam auf den niederen Speiseröhrenschliessmuskeldruck wurde mittels einer wahllosen Doppelblindstudie mit neun gesunden Freiwilligen untersucht. Es ergab sich dabei eine kleine aber statistisch bedeutsame Abnahme des Schrankendrucks. Die Abnahme des Schrankendrucks stand in keinerlei Beziehung zu dem Schläfrigkeitsgrad.

EFFECTO DEL DIAZEPAN ORAL SOBRE LA PRESION DEL ESFINTER INFERIOR DEL ESOFAGO

SUMARIO

Se investigó el efecto de 10 mg de diazepan oralmente administrados, en relación a la presión del esfinter inferior del esófago, siguiendo un estudio aleatorio de doble anonimato efectuado en nueve voluntarios sanos. La presión obstáculo disminuyó ligeramente, pero alcanzando un grado estadístico significativo. La reducción de dicha presión no vino relacionada con el nivel de somnolencia.

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USE OF PENTOLINIUM IN POSTOPERATIVE HYPERTENSION RESISTANT TO SODIUM NITROPRUSSIDE

R. M. JONES, C. B. HANTLER AND P. R. KNIGHT

SUMMARY

Five patients with systemic arterial hypertension occurring in the postoperative period and resistant to sodium nitroprusside are described. The hypertension was associated with evidence of increased activity of the autonomic and renin–angiotensin systems. Sympathetic blockade using the ganglion blocking agent, pentolinium, enabled the arterial pressure to be controlled adequately in all patients. This was associated with a decrease in catecholamine concentrations, plasma renin activity and angiotensin II concentrations.

An increase in arterial pressure in the period following operation may be disadvantageous, particularly to patients with arteriosclerotic vascular disease, since the increase in afterload may adversely affect cardiac function and myocardial oxygen requirements. Control of arterial pressure is important and, despite adequate analgesia, many patients require additional measures to modify those changes in arterial pressure observed following surgery. This report describes the clinical features and management of five patients, whose arterial pressure remained increased following surgery.

REPORTS OF FIVE PATIENTS

Patient 1. A 63-yr-old white female underwent aortic–bifemoral anastomosis. Before surgery the patient received hydrochlorothiazide for the treatment of mild hypertension. Adult onset diabetes mellitus was controlled by diet. Following surgery an i.v. infusion of sodium nitroprusside (SNP) could not decrease arterial pressure below 180/100 mm Hg. The administration of pentolinium 3 mg i.v. decreased the arterial pressure to 130/80 mm Hg.

Patient 2. A 56-yr-old white male with mild hypertension controlled with hydrochlorothiazide, and increased concentration of serum lipid, underwent carotid endarterectomy. During SNP infusion after operation a value of arterial pressure as great as 210/120 mm Hg was recorded. The administration of pentolinium 7 mg i.v. decreased arterial pressure to 150/85 mm Hg.

Patient 3. A 37-yr-old white female underwent clipping of a cerebral arterial aneurysm. The patient had no other known disorder. The postoperative arterial pressure was 160/100 mm Hg during an infusion of SNP. After administration of pentolinium 5 mg i.v. arterial pressure decreased and was maintained at 100/60 mm Hg.

Patient 4. A 60-yr-old white male underwent coronary artery bypass surgery for triple vessel occlusive disease. The patient was taking propranolol 20 mg four times a day for control of angina. During an infusion of SNP his arterial pressure was 190/115 mm Hg. Following pentolinium 2.5 mg i.v. this decreased to 135/85 mm Hg.

Patient 5. A 66-yr-old white male underwent coronary artery bypass surgery for triple vessel occlusive disease. Propranolol 20 mg four times a day was administered before operation to control angina. The arterial pressure during the infusion of SNP in the period after operation was 185/110 mm Hg. Pentolinium 3 mg i.v. decreased the arterial pressure to 140/90 mm Hg.

Hypertension was present immediately following surgery in all these patients, despite what was judged to be adequate analgesia. Blood-gas tensions and the concentrations of the serum electrolytes and blood glucose were within normal limits during the administration of the SNP. Patients 1–3 had residual neuromuscular blockade secondary to pancuronium antagonized with neostigmine and were breathing supplementary oxygen from a face mask. These three patients had normal Pa_{CO_2}

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values. Both of the patients who underwent coronary artery bypass (Nos 4 and 5) received mechanical ventilation of the lungs after operation because of the residual effects of diazepam and morphine anaesthesia. All five patients had indwelling arterial cannulae which permitted continuous monitoring of arterial pressure.

The infusion of SNP was started at $0.5\,\mu g\,kg^{-1}\,min^{-1}$ and increased slowly. These patients remained hypertensive at the maximum infusion rate of SNP considered to be safe at this institution ($8\,\mu g\,kg^{-1}\,min^{-1}$). The decision to change therapy was made 15 min after this rate of infusion had failed to decrease the arterial pressure to the desired value. Pentolinium was given in 0.5-mg increments i.v., every 5–10 min, until the desired arterial pressure was achieved.

METHODS

Blood samples were taken 15 min after the institution of SNP with the vasodilator being infused at the maximum rate ($8\,\mu g\,kg^{-1}\,min^{-1}$). Samples were repeated 30–45 min later after the arterial pressure had been stabilized for 15 min following the administration of pentolinium. Plasma catecholamine concentrations (adrenaline, noradrenaline and dopamine), plasma renin activity and angiotensin II concentrations were measured. The concentrations of adrenaline, noradrenaline and dopamine were determined by the radio-enzymatic method of Peuler and Johnson (1977). Plasma renin activity was determined by radioimmunoassay, using a commercially available kit (RIA-New England Nuclear, Medical Diagnostics Division, North Billerica, Massachusetts 01862). Angiotensin II concentration was measured by the radioimmunoassay technique described by Nicholls and Espiner (1976).

RESULTS

Pentolinium provided smooth control of the increases in arterial pressure in these five patients. Table I summarizes the results and shows the arterial pressures and heart rates, noted at the time of withdrawal of the blood samples.

The plasma adrenaline concentration was similar ($P > 0.2$) in the two samples. The plasma concentrations of noradrenaline, dopamine and angiotesin II, and the renin activity, were reduced ($P < 0.05$) after the administration of pentolinium, when compared with samples taken during the infusion of SNP.

DISCUSSION

Increases in arterial pressure following the termination of surgery and anaesthesia are common (Cormack, 1980) and may be marked. Autonomic tone and renin–angiotensin activity may be increased because of the physiological changes present following operation. These changes are associated particularly with vascular and cardiac procedures and include baroreceptor dysfunction (Bove et al., 1979) with sympathetic lability following carotid endarterectomy, as well as sympathetic overactivity (Fouad, Estafanous and Tarazi, 1978) associated with hypothermia, anaemia and the low output states which can follow myocardial revascularization.

Uncontrolled hypertension may be disadvantageous to the patient with arteriosclerotic cardiovascular disease; cardiac function may be adversely affected and myocardial oxygen demand increased secondary to the increase in afterload. The importance of control of arterial pressure in such patients during surgery, using agents which decrease pre-load primarily, has been emphasized (Jones, Knight and Hill, 1980). In addition, cerebral vascular accidents and bleeding from the suture lines in major arteries may result from increases in arterial pressure in the period after operation. Hypertension may increase intracranial pressure in those neurosurgical patients in whom cerebral oedema and impaired autoregulation of cerebral blood flow are present.

Sodium nitroprusside is used widely to control arterial pressure following surgery since minute-to-minute control of arterial pressure is possible. However, certain patients are resistant to SNP. An increase in cardiac output (Wildsmith et al., 1973) because of increases in heart rate and myocardial contractility secondary to autonomic activation, may explain these cases of resistance (Miller et al., 1977). Resistance to the action of SNP may be more likely after vascular and cardiac procedures, at a time when an increase in sympathetic activity is known to occur. Because of the danger of cyanide toxicity, which is related to the rate of infusion (Vesey and Cole, 1975), and the total dose administered, McDowell and colleagues (1974) recommended the use of an alternative method to control the arterial pressure in patients resistant to SNP. In none of the patients reported could the arterial pressure be controlled satisfactorily by the infusion of up to $8\,\mu g\,kg^{-1}\,min^{-1}$ of SNP. During infusion, the plasma concentrations of adrenaline,

TABLE I. *Haemodynamic and hormone values (mean ± SEM) during the infusion of sodium nitroprusside and after the administration of pentolinium. AP = arterial pressure (mm Hg); HR = heart rate (beat min^{-1}); RPP = rate pressure product; SNP = sodium nitroprusside. †Normal values for plasma renin activity and angiotensin II are for the rested, supine patient. *Significantly different (P < 0.05) from value during SNP infusion*

	AP	HR	RPP	Adrenaline (pg ml^{-1})	Noradrenaline (pg ml^{-1})	Dopamine (pg ml^{-1})	Plasma renin activity (ng ml^{-1} h^{-1})	Angiotensin II (pg ml^{-1})
Normal values	—	—	—	30–100	150–250	0–100	0.6–4.0†	20–50†
SNP	185/109	105	19530	141.2	515.8	49.6	11.4	96.4
	(8/4)	(7)	(1734)	(40.6)	(95.6)	(7.7)	(2.4)	(20.5)
Pentolinium	131/80	96	12635	64.2	119.6*	18.0*	2.4*	23.9*
	(9/5)	(4)	(1054)	(7.0)	(12.4)	(7.2)	(0.2)	(4.6)

noradrenaline, dopamine and angiotensin II were increased, as was renin activity. It is not possible to ascribe with certainty the increases in these concentrations to the infusion of SNP, as we did not measure the values before the start of the infusion. However, ganglionic blockade with pentolinium enabled us to control the arterial pressure in all the patients. This was associated with a significant ($P < 0.05$) decrease in the plasma concentrations of noradrenaline, dopamine, renin and angiotensin II compared with the concentrations assayed during the infusion of SNP (table I). Plasma adrenaline concentration also decreased to within the normal range, although the change was not statistically significant.

The ability of pentolinium to inhibit the release of catecholamines in the period after operation is of importance. It might be anticipated that the decrease in arterial pressure produced by pentolinium would be associated with changes in renal afferent arteriolar tone and activation of the renin–angiotensin system. However, Keeton and Pettinger (1979) have suggested that changes in renin by drug-induced hypotension is primarily a result of autonomic reflex, via the carotid barosystem. They demonstrated that the release of renin by drug-induced hypotension is primarily a result of autonomic reflex, via the carotid baroreceptors and renal sympathetic nerves. These impulses would be blocked by pentolinium. Our results support their findings.

We conclude that the control of arterial pressure following operation using pentolinium is associated with a decrease in the concentration of noradrenaline, dopamine, plasma and angiotensin II, and renin activity. These results suggest inhibition of autonomic tone and suppression of the renin–angiotensin–aldosterone axis by this drug. Control of arterial pressure with pentolinium during this period may be more suitable in patients in whom activation of these two systems is likely to occur.

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USAGE DU PENTOLINIUM POUR L'HYPERTENSION POSTOPERATOIRE RESISTANT AU NITROPRUSSIATE DE SODIUM

RESUME

Cinq patients souffrant d'hypertension artérielle systémique se produisant dans la phase postopératoire et résistant au nitroprussiate de sodium, sont décrits dans cet article. L'hypertension a été associée à la présence d'une activité accrue des systèmes nerveux sympathique et de rénine–angiotensine. Le blocage sympathique à l'aide du pentolinium, agent de blocage du ganglion, a permis de contrôler la tension artérielle d'une manière adéquate chez tous les patients. Ceci a été associé à une diminution des concentrations de catécholamines, de l'activité rénine et des concentrations d'angiotensine II dans le plasma.

DIE ANWENDUNG VON PENTOLINIUM BEI POSTOPERATIVER HYPERTONIE, DIE AUF NITROPRUSSIDNATRIUM NICHT REAGIERT

ZUSAMMENFASSUNG

Es werden fünf Patienten mit systemischer arterieller Hypertonie während der postoperativen Periode beschrieben, die auf Nitroprussidnatrium nicht reagierte. Die Hypertonie war mit Anzeichen einer gesteigerten Aktivität der autonomen und Chymosin–Angiotensin-Systeme verbunden. Blockade des sympathischen Nervensystems mittels des Ganglienblockierungsmittels Pentolinium ermöglichte eine hinreichende Beeinflussung des Arteriendrucks bei allen Patienten. Dies war mit einer Abnahme der Brenzkatechinäthanolamin-Konzentration, der Plasmachymosin-Aktivität und der Angiotensin II-Konzentration verbunden.

USO DEL PENTOLINO PARA LA HIPERTENSION POSTOPERATORIA RESISTENTE AL NITROPRUSIATO DE SODIO

SUMARIO

Se describen cinco pacientes con hipertensión sistémica arterial resistente al nitroprusiato, habiendo ocurrido dicha hipertensión durante el periodo postoperatorio. La hipertensión vino asociada con la evidencia de un incremento en la actividad de los sistemas autonómicos y de renina–angiotensina. El bloqueo simpático, usando el agente de bloqueo del ganglio, el pentolino, hizo posible el controlar adecuadamente la presión arterial de todos los pacientes. Esto vino asociado con una disminución en las concentraciones de catecolamina, de la actividad de la renina en el plasma y de las concentraciones de angiotensina II.

Br. J. Anaesth. (1981), 53, 1155

EFFECT OF HIGH-DOSE FENTANYL ANAESTHESIA ON THE METABOLIC AND ENDOCRINE RESPONSE TO CARDIAC SURGERY

E. S. WALSH, J. L. PATERSON, J. B. A. O'RIORDAN AND G. M. HALL

SUMMARY

The effect of high-dose fentanyl anaesthesia ($75\,\mu g\,kg^{-1}$) on the metabolic and endocrine responses to cardiac surgery was compared with results obtained in similar patients who had received incremental doses of papaveretum. High-dose fentanyl anaesthesia prevented the increases in blood glucose, plasma cortisol and plasma growth hormone concentrations found before cardiopulmonary bypass, but during cardiopulmonary bypass was only effective in decreasing the hyperglycaemia. The continued administration of fentanyl following operation failed to suppress the hormonal and metabolic changes so that the total urinary excretion during the first 5 days after surgery was similar in both groups of patients. High-dose fentanyl anaesthesia was associated with only transient metabolic benefits confined to the period during operation.

There has been considerable interest recently in the use of high-dose fentanyl anaesthesia to decrease or abolish the metabolic and endocrine responses to surgery (Editorial, 1979; Editorial, 1980). Although Hall and colleagues (1978) showed that fentanyl $50\,\mu g\,kg^{-1}$ body weight abolished the changes in plasma cortisol, growth hormone (GH), and blood glucose concentrations associated with prolonged pelvic surgery, Cooper and co-workers (1981), also using fentanyl $50\,\mu g\,kg^{-1}$ for gastric surgery, observed only a transient decrease in the metabolic and hormonal changes.

Stanley and colleagues have undertaken several studies using high-dose fentanyl for cardiac surgery and claim that the technique improves cardiovascular stability (Stanley and Webster, 1978; Lunn et al., 1979; Stanley, Philbin and Coggins, 1979). More recent work by this group has shown that fentanyl $75\,\mu g\,kg^{-1}$ abolished the plasma noradrenaline, adrenaline and cortisol responses to cardiac surgery until the onset of cardiopulmonary bypass (CPB) (Stanley et al., 1980).

The purpose of the present study was to compare the effects of the supplementation of nitrous oxide and oxygen anaesthesia with either high-dose fentanyl (total dose $75\,\mu g\,kg^{-1}$) or intermittent papaveretum on the metabolic and endocrine responses associated with aortic valve replacement. Unlike previous studies of high-dose fentanyl we continued the administration of fentanyl into the period after operation in an attempt to suppress the catabolic changes. The observations were extended to the first 5 days after operation, during which nitrogen balance studies were undertaken to compare the loss of muscle protein in the two groups of patients.

PATIENTS AND METHODS

The experimental plan was based on that used by Brandt and colleagues (1978) to examine the effects of high-dose morphine anaesthesia ($4\,mg\,kg^{-1}$ body weight) on the metabolic response to cardiac surgery.

Patients

Sixteen patients with aortic valve disease were investigated. They were otherwise healthy and not suffering from endocrine or metabolic disease nor taking drugs known to alter metabolism. The patients were allocated randomly to receive either increments of papaveretum as indicated clinically (the standard technique for cardiac surgery in this hospital for many years) or fentanyl to a total dose of $75\,\mu g\,kg^{-1}$. All patients gave written informed consent to the study which was approved by the Ethics Committee of Hammersmith Hospital. On the day before surgery the skinfold thicknesses and the arm circumference of the patients were

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measured to calculate the percentage of fat to body weight and the arm muscle area (Gurney and Jelliffe, 1973; Durnin and Womersley, 1974). These measurements were repeated on the 7th day following surgery.

Anaesthesia

The patients were premedicated with droperidol 2.5–5 mg, papaveretum 10–20 mg and hyoscine 0.2–0.4 mg i.m. 90 min before surgery. On arrival in the anaesthetic room, a central venous catheter was inserted percutaneously via a vein in an antecubital fossa for the collection of blood samples. Anaesthesia was induced with a dose of thiopentone sufficient to abolish the eyelash reflex, the trachea was intubated following the administration of pancuronium and the lungs ventilated with nitrous oxide and oxygen. Arterial and internal jugular cannulae, a urinary catheter and oesophageal and rectal temperature probes were inserted. Anaesthesia was supplemented in eight patients with increments of papaveretum (mean total dose 0.91 $mg\,kg^{-1}$, SEM ± 0.12), while the remainder received fentanyl 50 $\mu g\,kg^{-1}$ at induction of anaesthesia and a further fentanyl 25 $\mu g\,kg^{-1}$ immediately before cardiopulmonary bypass (CPB). Ventilation was adjusted to maintain Pa_{CO_2} in the range 4.5–5.0 kPa. Approximately 1000 ml of Hartmann's solution was infused i.v. between the induction of anaesthesia and the start of CPB.

Cardiopulmonary bypass

Heparin 3 $mg\,kg^{-1}$ was administered i.v. to allow cannulation of the aorta and vena cavae. An American Optical Pump with either a Shiley or Rygg oxygenator was used. The priming fluid consisted of 2 litre of Hartmann's solution and sodium bicarbonate 25 mmol. The patients were cooled to 28 °C and myocardial preservation undertaken with 1–2 litre of ice-cold cardioplegic solution into the root of the aorta or coronary arteries. On completion of the valve replacement the patients were rewarmed, the heart restarted, and when an adequate cardiac output was achieved, CPB was discontinued. Protamine sulphate 3 $mg\,kg^{-1}$ was administered i.v. to restore normal coagulation after the removal of the aortic and caval cannulae.

Postoperative management

Following CPB blood was transfused according to the cardiovascular status and the blood loss. An infusion of sodium nitroprusside (SNP) was required in one patient in each group and an infusion of dopamine was necessary in one patient in the papaveretum group.

On return to the intensive care unit artificial ventilation of the lungs was continued in all patients. Further analgesia and sedation were provided for patients in the papaveretum group by the administration of increments of papaveretum and diazepam i.v. as required (mean total doses of 29.4 mg ± SEM 6.8 mg and 9.7 mg ± SEM 3.5 mg respectively). The fentanyl group received fentanyl 0.5 µg i.v. every hour for the first 12–18 h following surgery. Blood and colloid were administered as necessary and a solution of 5% dextrose in water infused i.v. at a rate of 30 $ml\,h^{-1}\,m^{-2}$ for 24 h (mean total glucose load 61 g, ± SEM 5 g). Six of the fentanyl group (four SNP and two pentolinium) and four of the papaveretum group (two SNP and two pentolinium) required treatment with anti-hypertensive agents. One patient in the papaveretum group received an infusion of dopamine to maintain an adequate cardiac output. Adequate spontaneous respiration was achieved in all patients on the morning after operation. Even in the fentanyl group extubation of the trachea was possible 4–6 h after the last dose of fentanyl. Patients were returned to the ward on the day following surgery and the intake of protein and calories recorded.

Analyses

Blood was collected at the times shown in table I and analysed in duplicate for glucose, glycerol, lactate, pyruvate, β-hydroxybutyrate, alanine and non-esterified fatty acids (NEFA) by methods described by Hall and colleagues (1978, 1980). The haematocrit was determined by the microcapillary method. The coefficients of variation for duplicate estimations were glucose 0.6%, alanine 0.8%, NEFA 0.8%, lactate, 1.6%, β-hydroxybutyrate 2.1% and pyruvate 4.5%. The concentrations of plasma cortisol, growth hormone (GH) and insulin were determined in duplicate by radioimmunoassay. The coefficients of variation for replicates within each assay were 2.6–7.1% for GH, 6.0–10.0% for insulin and 6.0% for cortisol. The between-batch quality control data showed coefficients of variations of 11.4 and 14.5% for insulin, 5.3 and 6.3% for GH and 10.3% for cortisol.

TABLE I. *Times of collection of blood samples (CPB = cardiopulmonary bypass)*

Sample	Time
A	Before induction of anaesthesia
B	After induction, before surgery
C	After 30 min surgery
D	After heparin, before CPB
E	After 20 min CPB
F	After 40 min CPB
G	After 60 min CPB
H	After CPB, before protamine
I	1 h after CPB
J	2 h after CPB
K	4 h after CPB
L	6 h after CPB
M	10.00 h on day 1
N	10.00 h on day 2
O	10.00 h on day 3
P	10.00 h on day 4
Q	10.00 h on day 5

TABLE II. *Anthropomorphic characteristics of patients (mean ± SEM)*

	Fentanyl ($n = 8$)	Papaveretum ($n = 8$)
Sex	6M, 2F	4M, 4F
Age (yr)	52.0±4.5	55.8±4.7
Weight (kg)	72.5±2.0	66.1±4.4
Body fat (%)	35.6±3.2	32.2±4.2

TABLE III. *Mean (± SEM) duration of anaesthesia and surgery (CPB = cardiopulmonary bypass)*

	Fentanyl	Papaveretum
Duration of anaesthesia before surgery (min)	37.5±1.9	33.6±1.8
Duration of surgery before CPB (min)	54.5±4.2	55.7±3.5
Duration of CPB (min)	72.3±6.4	85.7±5.5
Duration of surgery after CPB (min)	68.9±6.4	67.9±7.1
Total surgery time (min)	195.7±8.9	209.3±8.6

An aliquot of urine was retained from each 24-h urine sample during the first 5 days after operation and analysed for total urinary nitrogen concentration by an automated Kjeldahl technique (Holbrook, 1979). Daily nitrogen balances were calculated from measured protein intake and urinary loss with corrections for altered blood urea if appropriate.

Statistics

Evaluation of the data was undertaken using a two-way analysis of variance with Duncan's multiple range test to determine the presence of significant changes with time from control values in each group. A hierarchical two-way analysis of variance was used to determine the presence of a significant difference between groups.

RESULTS

The anthropomorphic characteristics of the patients and the duration of anaesthesia and surgery are shown in tables II and III respectively. There was no significant difference between the two groups.

A complete table of the results (metabolites, hormones and haematocrits) is available from the authors.

Glucose and gluconeogenic precursors

The blood glucose concentration increased progressively in the papaveretum group from 4.18 mmol litre^{-1} before the induction of anaesthesia to 9.20 mmol litre^{-1} ($P<0.01$) after 60 min of CPB (fig. 1). In the fentanyl group the glycaemic response to surgery before CPB was abolished and the response to CPB was only 6.19 mmol litre^{-1} after 60 min ($P<0.01$). There was a significant decrease ($P<0.01$) in blood glucose concentration in the fentanyl group compared with the papaveretum group from 30 min of surgery until 2 h after CPB. After this time the glycaemic response was similar in both groups and a normal blood glucose concentration was found from the 2nd day after operation onwards.

Blood lactate concentrations increased significantly ($P<0.01$) in both groups during surgery, CPB and in the period after operation (fig. 2). The hyperlactataemia in the papaveretum patients was significantly greater ($P<0.05$) than that demonstrated in fentanyl patients after 40 min of CPB, immediately after CPB, and 1, 4 and 6 h after CPB. There was no significant change in blood pyruvate and alanine concentrations during the study although the increases in the concentrations of pyruvate and alanine in the papaveretum group only just failed to reach statistical significance ($P<0.1$) (figs 3 and 4). Comparison between the groups, however, showed a significant decrease ($P<0.05$) in the pyruvate concentration in the fentanyl patients 1 h after CPB and in the alanine values 6 h after CPB and on the 1st and 3rd days after operation.

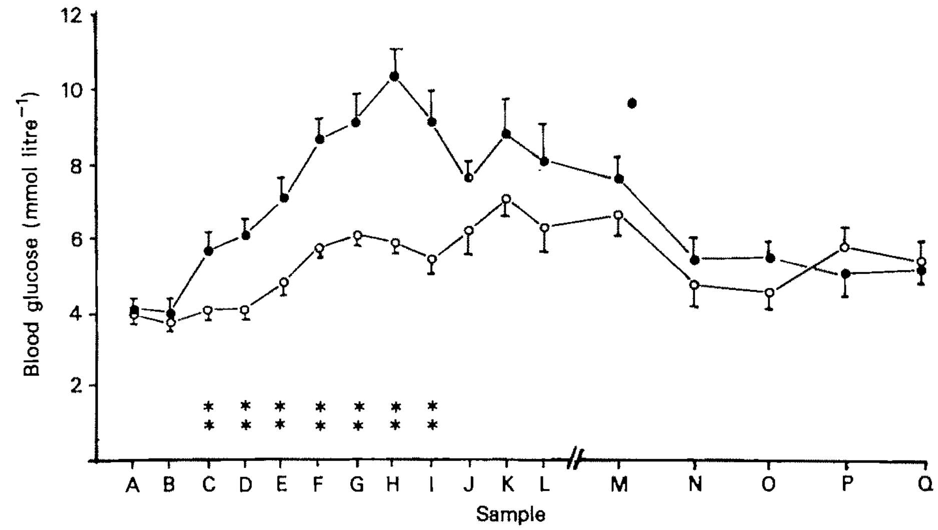

FIG. 1. Mean (and SEM) blood glucose concentrations in papaveretum group (closed circles) and fentanyl group (open circles). Significant difference between the two groups shown by ** ($P<0.01$).

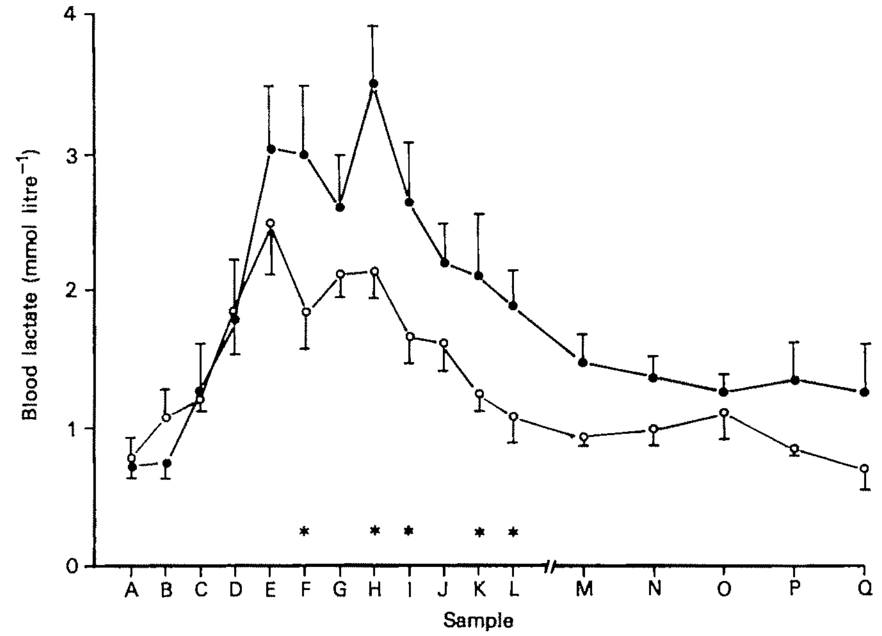

FIG. 2. Mean (and SEM) blood lactate concentrations in papaveretum group (closed circles) and fentanyl group (open circles). Significant difference between the two groups shown by * ($P<0.05$).

Fat metabolism

Heparinization was associated with a significant increase ($P<0.01$) in NEFA concentrations in both groups of patients which persisted throughout CPB ($P<0.05$) (fig. 5). NEFA concentrations decreased significantly ($P<0.01$) below control values on the 3rd, 4th and 5th day after operation. The changes in plasma glycerol concentration were similar to those observed for NEFA with peak values occurring after heparin ($P<0.01$) and

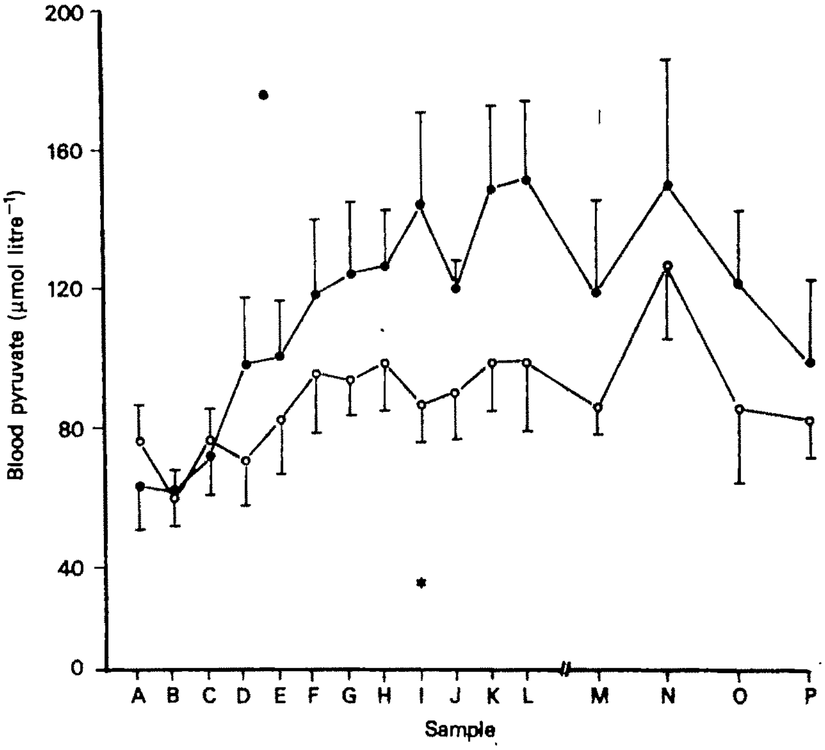

FIG. 3. Mean (and SEM) blood pyruvate concentrations in papaveretum group (closed circles) and fentanyl group (open circles). Significant difference between the two groups shown by * ($P<0.05$).

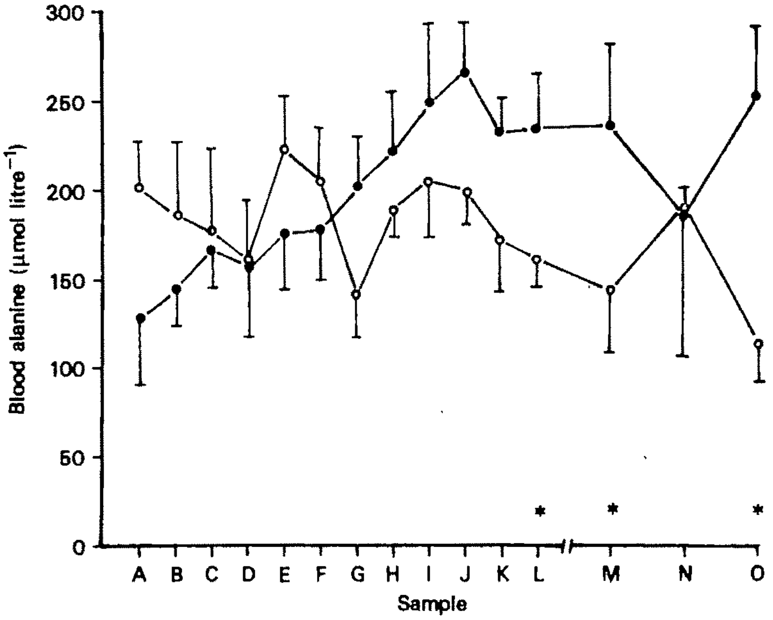

FIG. 4. Mean (and SEM) blood alanine concentrations in papaveretum group (closed circles) and fentanyl group (open circles). Significant difference between the two groups shown by * ($P<0.05$).

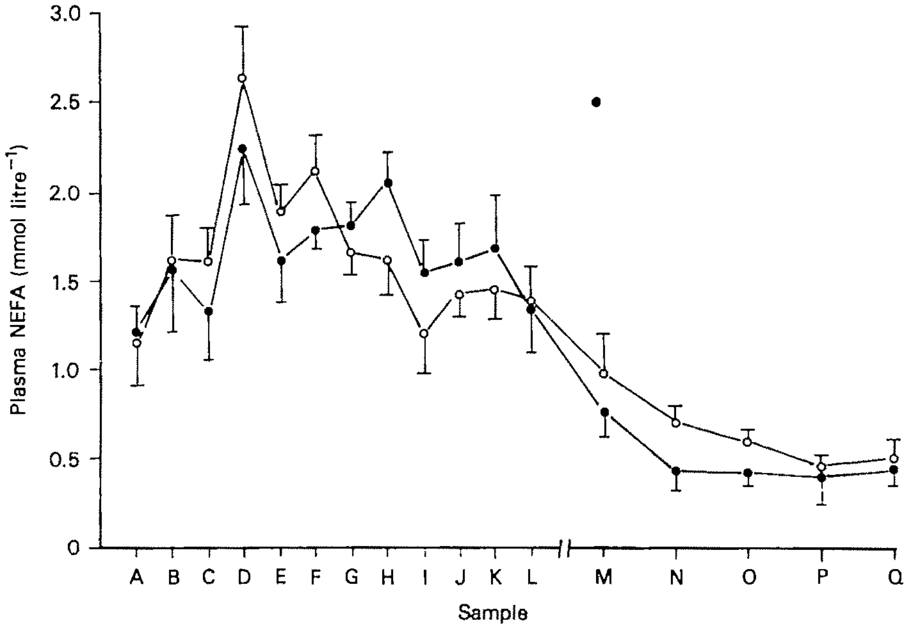

FIG. 5. Mean (and SEM) plasma NEFA concentrations in papaveretum group (closed circles) and fentanyl group (open circles).

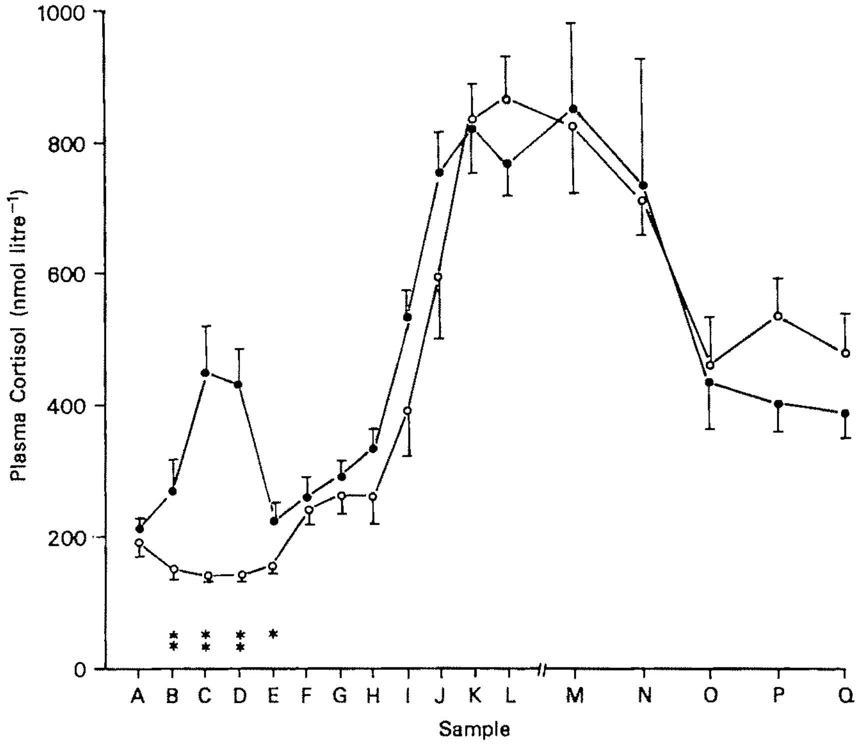

FIG. 6. Mean (and SEM) plasma cortisol concentrations in papaveretum group (closed circles) and fentanyl group (open circles). Significant difference between the two groups shown by * ($P<0.05$) and ** ($P<0.01$).

a decrease in the period after operation ($P<0.05$) (results not shown). There were no changes in blood β-hydroxybutyrate concentrations throughout the study (results not shown).

Hormonal changes

The plasma cortisol concentration increased with surgery in the papaveretum group to 430 nmol litre^{-1} after heparin ($P<0.05$), but decreased to only 220 nmol litre^{-1} after 20 min of CPB (fig. 6). The abrupt decrease in cortisol concentration was associated with the haemodilution as shown by a concomitant change in haematocrit from 35.4% to 25.4%, The plasma cortisol concentration then increased slowly after CPB so that the maximum value of 849 nmol litre^{-1} was found on the 1st day after operation. The increase in the cortisol concentration persisted throughout the postoperative period and was still significantly increased ($P<0.05$) on the 5th day. In the fentanyl group there was a significant decrease in cortisol concentration with the onset of surgery to reach 140 nmol litre^{-1} after heparin ($P<0.01$). However, with the onset of CPB the pattern of the cortisol response was similar to that found in the papaveretum group, including a significantly increased ($P<0.05$) value of 477 nmol litre^{-1} on the 5th day after operation. Thus, the cortisol response associated with fentanyl was only decreased significantly compared with the papaveretum group after the induction of anaesthesia, 30 min of surgery and after heparinization ($P<0.01$), and after 20 min of CPB ($P<0.05$).

Plasma GH concentration increased in the papaveretum group after 30 min of surgery to 11.1 mu. litre^{-1} ($P<0.05$) and this significant increase persisted until the 2nd day after operation (fig. 7). The GH response to surgery was suppressed in the fentanyl group but increased with the onset of CPB to become significant after 40 min (9.1 mu. litre^{-1}; $P<0.05$). This increase persisted in a similar pattern to the papaveretum patients. In spite of the initial suppression of GH in those patients given fentanyl there was no significant difference between the two groups ($P<0.1$).

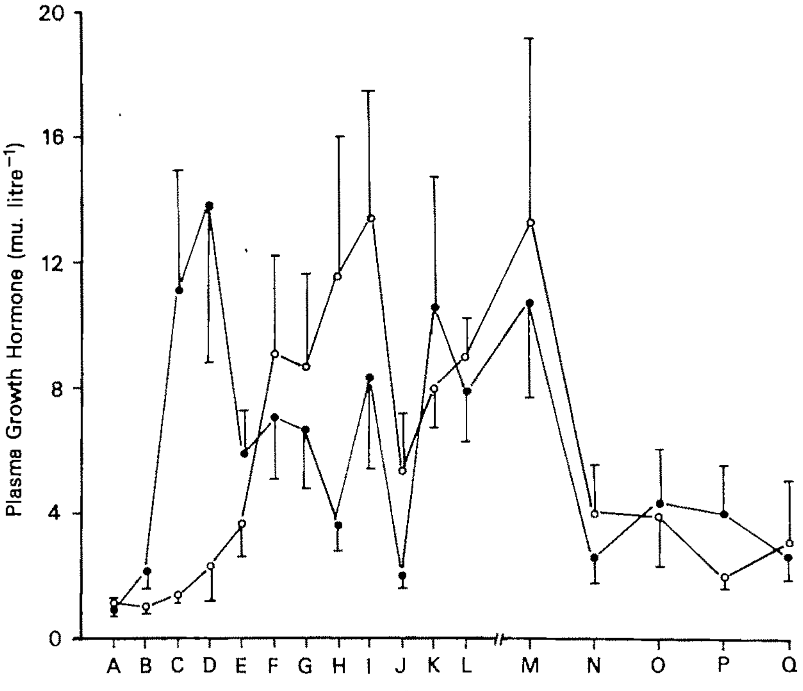

FIG. 7. Mean (and SEM) plasma growth hormone concentrations in papaveretum group (closed circles) and fentanyl group (open circles).

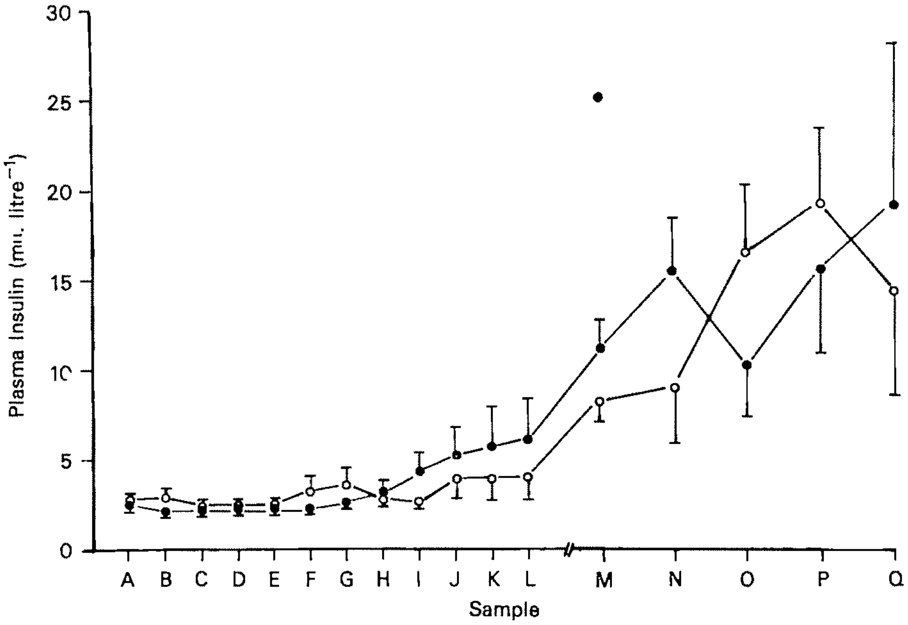

FIG. 8. Mean (and SEM) plasma insulin concentrations in papaveretum group (closed circles) and fentanyl group (open circles).

Control insulin values were very small in both groups of patients (2.6 mu. litre^{-1}) and insulin suppression persisted throughout surgery and CPB (fig. 8). Insulin concentrations increased slightly after surgery but this only became significant ($P<0.01$) on the 1st day after operation.

Nitrogen excretion

The mean total urinary nitrogen excretion for the first 5 days after operation was 47.3 g (SEM ± 4.6 g) for the fentanyl group and 42.1 g (SEM ± 6.2 g) for the papaveretum group. This was equivalent to a mean cumulative urinary nitrogen excretion of 0.66 g kg^{-1} body weight (SEM ± 0.06) and 0.64 g kg^{-1} body weight (SEM ± 0.09) respectively.

There was a simlar decrease in the muscle arm area in both groups during the first 7 days after surgery, from 48.8 cm^2 to 43.0 cm^2 in the fentanyl patients and from 44.2 cm^2 to 40.5 cm^2 in the papaveretum patients.

DISCUSSION

The results show that high-dose fentanyl anaesthesia has only limited effects on the metabolic and hormonal responses to cardiac surgery and that these effects are confined to the period before and during CPB. After CPB the pattern of the response was similar in both groups of patients and was reflected by the failure to show any difference in nitrogen balance or loss of arm muscle area. It must be emphasized that it was not possible to control rigidly the management of the patients after CPB. Blood transfusion and the administration of antihypertensive and inotropic agents was undertaken according to the clinical requirements of the patients and must have contributed to some extent to the changes observed in circulating metabolites. For example, typical metabolite values for 5-day-old stored blood were in the ranges glucose 9.6–18.9 mmol litre^{-1}, lactate 6.13–9.79 mmol litre^{-1}, pyruvate 241–335 μmol litre^{-1} and alanine 11–110 μmol litre^{-1}. We consider it is unlikely, however, that any difference in clinical management between the two groups of patients was responsible for the failure of fentanyl to decrease the metabolic and endocrine changes after CPB. The results demonstrate clearly that the increases in plasma cortisol, GH and blood glucose concentrations in the high-dose fentanyl patients started during CPB.

The hyperglycaemia found in the papaveretum group was similar to that observed by Nuutinen and colleagues (1977) and Brandt and co-workers (1978), but was considerably less than the observations by other workers who incorporated 5%

dextrose in the pump priming fluid (Allison, 1971; Hewitt et al., 1972; Hill, Sönksen and Braimbridge, 1974; Yokota et al., 1977). The cause of the decrease in the glycaemic response to surgery and CPB in the fentanyl group is not apparent from the hormonal changes that were measured. Although fentanyl abolished the cortisol and GH responses to surgery before CPB, this was not sustained and there was no difference in plasma insulin values between the two groups (figs 6, 7 and 8). The other catabolic hormones capable of inducing an increase in blood glucose concentration are the catecholamines and pancreatic glucagon. Stanley and associates (1980) found that fentanyl 75 μg kg^{-1} prevented an increase in circulating noradrenaline and adrenaline before CPB but that the concentrations of the catecholamines increased significantly during CPB. It is possible, however, that high-dose fentanyl decreases the adrenergic response to CPB as Stanley and colleagues (1980) did not include any other anaesthetic techniques for comparison. The role of glucagon in this glycaemic response has not been investigated, but the available evidence suggests that its effect on increasing hepatic glucose output is likely to be neither large or prolonged (Sherwin, Wahren and Felig, 1976).

The relative contributions of an increase in hepatic glycogenolysis and gluconeogenesis, and a decrease in peripheral glucose utilization to the hyperglycaemia of CPB remains to be elucidated. The high NEFA concentrations during CPB will have a glucose-sparing effect by acting as an alternative substrate for aerobic tissues (Newsholme, 1976). The failure of insulin secretion to respond to the hyperglycaemia of CPB (fig. 8) will also impair glucose utilization, and is considered by Allison (1971) to be a result of the predominance of α-inhibitory effects of increased sympathetic activity. Whatever the precise mechanism of the hyperglycaemia, the mean blood glucose concentration of 10.47 mmol litre^{-1} observed in the papaveretum group immediately after CPB was sufficiently increased to produce glycosuria in patients with a normal renal threshold.

Heparin is a potent stimulator of the enzyme lipoprotein lipase (Heaf et al., 1977) so that the use of this drug for anticoagulation before CPB is associated with a profound increase in circulating NEFA concentrations (fig. 5). The timing of the increase in NEFA immediately before aortic cross-clamping is unfortunate as the work of Opie and colleagues suggests that high plasma NEFA concentrations are associated with an extension of myocardial ischaemia both experimentally and clinically (de Leiris, Opie and Lubbe, 1975; Opie, Tansey and Kennelly, 1977). The development of a different anticoagulant, such as prostacyclin, which does not have this undesirable side-effect, would be advantageous.

This study afforded an excellent opportunity to study any toxic effects of the administration of high doses of fentanyl. The maximum total dose received by a patient in the fentanyl group was 14.25 mg in 18 h. In the period after operation acute tolerance developed to both the respiratory depressant and analgesic effects of fentanyl so that it was comparatively easy to establish adequate spontaneous respiration 4–6 h after the last dose of fentanyl. Similar tolerance to fentanyl has been observed recently in rats (Colpaert et al., 1980) and our findings suggest that the relationship of clinical effects, such as respiratory depression, to a given dose of fentanyl may be influenced profoundly by previous, repeated administrations of the drug. Two patients developed occasional flexion of the arms when asleep during the first 2 days after operation, but this disappeared on waking. There were no other problems during the period after operation.

In conclusion, the results of this study, taken in conjunction with those of Brandt and co-workers (1978) and Stanley and colleagues (1980), show that there is, at present, no anaesthetic technique capable of abolishing the endocrine and metabolic response to CPB. It is not known which of the profound physiological changes associated with CPB is responsible for evoking the hormonal changes, although several of these factors, such as hypothermia, haemodilution and non-pulsatile flow, can be investigated experimentally. When the role of the various physiological stimuli of CPB have been defined, it may then be possible to devise a suitable anaesthetic technique to abolish the metabolic and hormonal response to cardiac surgery.

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EFFETS DE L'ANESTHESIE INDUITE PAR DE FORTES DOSES DE FENTANYL SUR LA REACTION METABOLIQUE ET ENDOCRINE A LA CHIRURGIE CARDIAQUE

RESUME

L'effet de l'anesthésie induite par de fortes doses de fentanyl ($75 \mu g\,kg^{-1}$) sur les réactions métaboliques et endocrine à la chirurgie cardiaque a été comparé aux résultats obtenus sur des patients similaires auxquels on avait administré des doses criossantes de papaveretum. L'anesthésie induite par de fortes doses de fentanyl a empêché l'augmentation de glucose dans le sang, de cortisol dans le plasma et des concentrations d'hormones de croissance dans le plasma que l'on trouve avant les dérivations cardiopulmonaires, mais qui ne sont efficaces pendant la dérivation cardiopulmonaire que pour faire diminuer l'hyperglycémie. La continuation de l'administration de fentanyl après l'intervention chirurgicale n'a pas supprimé les changements hormonaux et métaboliques de sorte que la totalité de l'excrétion urinaire au cours des cinq premiers jours qui ont suivi l'opération a été similaire dans les duex groupes de patients. L' anesthésie induite par de fortes doses de fentanyl n'a été associée qu'à des avantages métaboliques transitoires, limités à la période nécessaire à l'intervention chirurgicale.

DIE AUSWIRKUNG VON EINER AUS GROSSEN DOSEN VON FENTANYL BESTEHENDEN ANÄSTHESIE AUF DIE METABOLISCHE UND ENDOKRINE REAKTION AUF HERZCHIRURGIE

ZUSAMMENFASSUNG

Die Auswirkung von einer aus grossen Dosen von Fentanyl bestehenden Anästhesie ($75 \mu g\,kg^{-1}$) auf die metabolische und endokrine Reaktion auf Herzchirurgie wurde mit den Ergebnissen von anderen Patienten verglichen, die gestufte Dosen von Papaveretum bekommen hatten. Die Fentanyl-Anästhesie verhinderte die Zunahme von Blutglukose- Plasmakortisol- und Plasmawachstumshormon-Konzentrationen vor kardiopulmonaler Umgehungschirurgie, aber während der kardiopulmonalen Umgehungschirurgie konnte sie nur eine Abnahme der Hyperglykämie bewirken. Die fortgesetzte Verabreichung von Fentanyl nach der Operation konnte die hormonalen und metabolischen Veränderungen

nicht unterdrücken, sodass die Gesamtharnausscheidung während der ersten 5 Tage nach der Chirurgie bei beiden Gruppen von Patienten vergleichbar war. Eine aus grossen Dosen von Fentanyl bestehende Anäthesie war mit nur vorübergehenden metabolischen Vorteilen verbunden, die auf die Dauer der Operation beschränkt waren.

CONSECUENCIAS DE LA ANESTESIA MEDIANTE UNA GRAN DOSIS DE FENTANILO EN LA RESPUESTA METABOLICA Y ENDOCRINA A LA CIRUGIA CARDIACA

SUMARIO

Se compararon los efectos de la anestesia efectuada con una gran dosis de fentanilo (75 $\mu g\,kg^{-1}$) sobre la respuesta metabólica y endocrina a la cirugia cardiaca, con los resultados obtenidos en pacientes similares que habian recibido dosis crecientes de papaveretum. La anestesia mediante una gran dosis de fentanilo impidió los incrementos de glucosa en la sangre, del cortisol en el plasma y el crecimiento de las concentraciones de hormonas en el plasma que se han encontrado en el lugar antes de efectuar la desviación cardiopulmonar, aunque durante dicha desviación su efectividad fue tan sólo en la disminución de hiperglicemia. La administración continua de fentanilo, después de la operación, no logró suprimir los cambios hormonales y metabólicos, de forma que la excreción urinaria total durante los cinco primeros dias que siguieron a la operación fue similar en ambos grupos de pacientes. La anestesia mediante grandes dosis de fentanilo vino asociada sólo con recuperaciones metabólicas temporales que se redujeron al período de la operación.

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PERCUTANEOUS PULMONARY ARTERY CATHETERIZATION VIA THE ARM BEFORE ANAESTHESIA: SUCCESS RATE, FREQUENCY OF COMPLICATIONS AND ARTERIAL PRESSURE AND HEART RATE RESPONSES

S. S. DE LANGE, M. J. BOSCOE AND T. H. STANLEY

SUMMARY

The success rate, frequency of complications and changes in systolic arterial pressure and heart rate during percutaneous pulmonary artery catheterization via an antecubital vein were evaluated before induction of anaesthesia in 84 patients about to undergo cardiac surgery. Serious complications were angina (2%) and a small tear in the tricuspid valve (one patient). If one of the basilic veins was used, the success rate was 93%. When it was necessary to use a cephalic vein, the success rate decreased to 60%. Overall success rate was 75%. Placing the catheter in the pulmonary artery resulted in an immediate increase in systolic arterial pressure in all patients and a significant increase in heart rate in patients not taking beta-adrenergic blocking drugs. This study demonstrates that percutaneous catheterization of the pulmonary artery via the basilic vein is a simple, safe, effective technique associated with few complications.

Catheterization of the pulmonary artery (PA) with a flow-directed balloon-tipped catheter via the internal jugular vein before anaesthesia is a common procedure in patients with cardiac disease about to undergo open heart operation (Pace, 1972; Katz et al., 1977; Kaplan, 1979; Lunn et al., 1979). However, this technique can increase systolic arterial pressure (SAP) and heart rate (HR) (Lunn et al., 1979) and is associated with a number of minor and some serious complications (Pace, 1972; Katz et al., 1977). Percutaneous catheterization of PA via the basilic vein in the right or left upper extremity is an alternative to catheterization via the internal jugular vein and might be less stressful and result in fewer complications. In this study the success and complication rates and arterial pressure and heart rate responses to percutaneous PA catheterization via the right basilic vein were determined in 84 unanaesthetized patients before valve replacement or coronary artery bypass operations.

METHODS

The plan of study was approved by the Leiden University Hospital Human Experimentation Committee. Informed consent for performance of the study was obtained from each patient at the time of the preoperative visit.

Patients were allocated to three groups according to their preoperative drug history and operation. Fifty-five patients were to undergo coronary artery bypass grafting (CABG) operations; 31 of these were taking propranolol or another beta-adrenergic blocking compound for angina or hypertension (group I) and 24 were not (group II). Twenty-nine patients were about to undergo valve replacement operations (group III).

Patients were premedicated with lorazepam 0.08 mg kg^{-1} orally 2 h and atropine 0.1 mg per 15 kg i.m. about 30 min before being taken to the operating room. Patients in group I received their usual morning dose of oral propranolol at the time of premedication. Upon arrival in the operating room, every patient had a 14-gauge catheter placed in a hand vein; saline 2–3 ml min^{-1} was infused and a bipolar lead II e.c.g. continuously recorded.

After the i.v. infusion was started, the left wrist was dorsiflexed and a 19- or 20-gauge catheter percutaneously introduced to the radial artery. Following this, the right antecubital fossa was inspected for evidence of a prominent basilic vein.

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(We did not distinguish between the median antecubital vein and basilic vein in this study because of the varying anatomy. Therefore catheterization was often accomplished via the median antecubital vein before it merged with the basilic vein. In all cases the catheter was eventually threaded through the basilic vein before entering the chest.) If a prominent basilic vein was present, the antecubital fossa was prepared with tincture of iodine solution, the skin over the vein anaesthetized with lignocaine and a Cordis introducer placed in the vein over a flexible stainless steel mini-guide wire previously implanted via a 16-gauge catheter. A flow-directed balloon-tipped thermodilution pulmonary artery catheter (Instrument Laboratories triple-lumen model 44166 7F) was then introduced to the right basilic vein through the Cordis introducer.

The catheter was then connected to a pressure transducer and advanced 40–45 cm. Following this, the balloon on the catheter tip was inflated and the catheter directed into the pulmonary artery using wave-form for location. If the catheter became lodged at the shoulder it was withdrawn 5–15 cm and re-advanced. If, after a few attempts, it remained impossible to pass the catheter beyond the shoulder, heparinized saline was injected through the distal aperture while advancing the catheter. If this failed, the balloon was gently inflated just before the obstruction and additional attempts made to advance the catheter while the patient was asked to take a deep breath. If it was impossible to flow-direct the catheter into the pulmonary artery within 30 min from skin puncture, the procedure was terminated and the attempt considered unsuccessful.

When a right basilic vein was neither visible nor palpable, the left basilic vein was inspected and used. If neither basilic vein could be found or was not prominent, the right cephalic vein was used and if the right cephalic vein was not prominent the left cephalic vein was used. If neither basilic nor cephalic veins were available, percutaneous pulmonary artery catheterization via the upper extremity was considered impossible and the attempt recorded as unsuccessful.

Systolic arterial pressure was measured with a Roche Arteriosonde (Model 1010) with a standard Riva Rocci cuff on the left arm and HR was determined by palpation at the right wrist. Arterial pressure and HR were recorded the night before operation, 2–4 min after entering the operating room, immediately after the catheter was placed in the radial artery and immediately following placement of the PA catheter. Patients were monitored continuously for signs of myocardial ischaemia (angina with or without depression of the ST segment on the e.c.g. of 1 mm or greater) during radial and pulmonary artery catheterization. E.c.g. was monitored continuously for ventricular extrasystoles, runs of ventricular tachycardia (three or more successive ventricular extrasystoles) and any other arrhythmia. Patients were visited on the 1st and 2nd days after operation and their antecubital fossa and neck areas inspected for haematoma and evidence of infection (redness, swelling, heat).

Haemodynamic data were analysed only in patients undergoing successful pulmonary artery catheterization. Data were analysed for significance using Student's paired *t* test for comparison with control values and analysis of variance for comparison with group II values. $P < 0.05$ was considered statistically significant.

RESULTS

All patients were either drowsy or sleeping upon arrival in the operating room, but were easily aroused. The three groups were similar with regard to age, weight and SAP and HR before operation (tables I and II).

TABLE I. *Responses of systolic arterial pressure (mm Hg) to radial and pulmonary arterial catheterization in 63 patients undergoing successful catheterization of the pulmonary artery (mean ± SD).* *P < *0.05*; †P < *0.025*; **P < *0.01*; *Student's paired* t *test when compared with control values*

	Preop. visit	Entrance to O.R.	Catheter in radial artery	Catheter in PA
Group I	121 ± 10	120 ± 9	128 ± 14	136* ± 15
Group II	126 ± 11	136* ± 14	140† ± 16	149** ± 18
Group III	123 ± 12	118 ± 14	127 ± 15	134* ± 17

TABLE II. *Responses of heart rate (beat min^{-1}) to radial and pulmonary arterial catheterization in 63 patients undergoing successful catheterization of the pulmonary artery (mean ± SD).* *P < *0.05*; *Student's paired* t *test when compared with control values*

	Preop. visit	Entrance to O.R.	Catheter in radial artery	Catheter in PA
Group I	63 ± 11	65 ± 10	67 ± 9	69 ± 11
Group II	67 ± 10	75 ± 13	76 ± 11	79* ± 14
Group III	72 ± 9	71 ± 8	73 ± 9	77 ± 11

A total of 57 patients had successful PA catheterization via either the right (50) or the left (seven) basilic veins (table III). Six additional patients had successful catheterization via the right or left cephalic veins. Four patients had unsuccessful basilic vein attempts and four had unsuccessful cephalic vein attempts at catheterization. In 11 patients either no upper extremity antecubital vein was available or the Cordis introducer could not be successfully introduced to a vein. Therefore, of the 71 patients in whom a PA catheter could be introduced to an upper extremity vessel in the antecubital fossa, 63 (89%) underwent successful catheterization within 30 min of starting the procedure.

TABLE III. *Number and percentage of 84 patients undergoing percutaneous pulmonary artery catheterization via the upper extremity with successful and unsuccessful results. *Percentage was computed by comparing the numbers of patients (No.) in which PA catheterization was successful with those in which it was not within a given category*

	Successful catheterization (No.)	(%)*	Unsuccessful catheterization (No.)	(%)*
Total patients	63	75	21	25
Basilic vein (R+L)	57	93	4	7
Right basilic	50	96	2	4
Left basilic	7	78	2	22
Cephalic vein (R+L)	6	60	4	40
Right cephalic	2	50	2	50
Cephalic + basilic	63	89	8	11
Group I	26	84	5	16
Group II	20	83	4	17
Group III	17	59	12	41

Patients in group II exhibited a significant increase in SAP on entering the operating room, a further increase after insertion of the radial artery catheter and a further increase after PA was entered (table I). Patients in groups I and III experienced no significant change in SAP until implantation of the PA catheter, when it became increased. Heart rate remained unchanged in groups I and III during the entire experiment, but became significantly increased in group II following catheterization of PA (table II).

Twelve of the 63 patients (19%) who had successful PA catheterizations via the upper extremity experienced at least one ventricular extrasystole or junctional beat during passage of the catheter through the right ventricle (table IV), but none exhibited ventricular tachycardia. Two patients, both in group II, experienced angina and e.c.g. evidence of myocardial ischaemia during the procedure. Breathing oxygen and temporary removal of the PA catheter from the heart cured the abnormality in both patients within 5 min and there was no recurrence on repeat catheterization.

None of the 84 patients in the study suffered haematoma of the neck, postoperative infection of the antecubital fossa, a knotted PA catheter, clot on the catheter upon removal, or a catheter that could not be removed at the end of the operation. No patient experienced a pulmonary artery laceration or a clinically significant air embolism or pneumothorax. However, six patients had an ante-

TABLE IV. *Complications of 84 patients undergoing percutaneous pulmonary artery catheterization via the upper extremity*

			Successful catheterization		Unsuccessful catheterization	
	Total	%	No.	%	No.	%
Ventricular extrasystole	14	17	12	19	2	10
Ventricular tachycardia	0	0	0	0	0	0
Angina	2	2	2	3	0	0
Haematoma (neck)	0	0	0	0	0	0
Haematoma (arm)	6	7	4	6	2	10
Antecubital infection	0	0	0	0	0	0
Pulmonary artery injury	0	0	0	0	0	0
Other cardiac injuries	0	0	0	0	1	5
Knotted PA catheter	0	0	0	0	0	0
Clot on catheter	0	0	0	0	0	0
Air embolism	0	0	0	0	0	0
Pneumothorax	0	0	0	0	0	0

cubital haematoma after operation and one sustained a tear in one of the leaflets of the tricuspid valve, discovered upon incision of the right ventricle, which required suturing.

DISCUSSION

Although flow-directed balloon-tipped pulmonary artery catheters were first implanted via a venous cutdown in the antecubital fossa (Swan et al., 1970), this technique is not often used in the operating room before induction of anaesthesia (Civetta and Gabel, 1972; Kaplan, 1979). The preferred method of insertion of PA catheters is usually by percutaneous catheterization of the internal jugular vein (IJV) in the neck using one of a variety of techniques for location of IJV and insertion of the catheter. Introduction of the PA catheter via IJV is said to be fast (average time of 15 min in experienced hands) and highly successful (97% success in one study; Zaidan et al., 1975). Introduction of PA catheter via IJV eliminates the difficulty of traversing the angle of the shoulder, which may occur with insertion through an arm vein, and allows a greater number of implanted PA catheters to be wedged in the lungs for measurement of pulmonary artery wedge pressure (Civetta and Gabel, 1972; Kaplan, 1979).

Unfortunately, insertion of a PA catheter via IJV results in many minor and some serious complications (Pace, 1972; Katz et al., 1977; Kaplan, 1979). Some of these, such as ventricular extrasystole and other arrhythmias, angina, injury of the pulmonary artery or other cardiac structures, pulmonary embolism or infarction, endocarditis and looping or knotting of the catheter, could and (as demonstrated in this study) do occur irrespective of the method of insertion of the catheter. Others such as laceration of the carotid artery or great veins in the neck, pneumothorax, air embolism, neck haematoma, infection, nerve damage in the neck and puncture of the trachea are unlikely with insertion techniques via an upper extremity and did not occur in this investigation. The frequency of these serious complications in PA catheterization via IJV is unknown but is obviously dependent upon the method with which IJV is catheterized, the puncture site and the experience and skill of the individual performing the procedure (Pace, 1972; Katz et al., 1977; Kaplan, 1979). Katz and coworkers (1977) reported a frequency of carotid puncture of 13% during attempts at locating IJV for PA catheterization. Belani and others (1980) reported that 12 of 125 attempts at IJV catheterization resulted in carotid puncture. In addition, these authors had one patient who sustained a pneumothorax and required thoracotomy, one with acute hydrothorax which required drainage and one with a paratracheal haematoma that resulted in phrenic nerve irritation (manifested by intermittent hiccup for 8 days). The serious complications in 14 of their 16 patients could be directly attributed to catheterization of the IJV and probably would never had occurred if insertion of the catheter had been made via a large peripheral vein.

When a suitably large antecubital vein was available in the present study, successful PA catheterization was achieved in 89% of attempts. If the right basilic vein was catheterized, the success rate increased to 96%. These results compare favourably with the 97% success rate of PA catheterization reported by Zaidan and others (1975) using IJV and are similar to those published by Swan and co-workers (1970) cutting down on an antecubital vein. Unfortunately, Swan and others (1970) did not report whether basilic, cephalic or both veins were used nor whether catheterization was attempted from the right or left arm. Our findings suggest that the basilic vein is superior to the cephalic and the right arm better than the left.

Another reported advantage of catheterization of PA via IJV rather than from a large peripheral vein is increased speed of insertion. Kaplan (1979) reported that the entire catheterization procedure via IJV averages approximately 15 min. There are no data to compare PA catheterization via IJV and the right basilic vein. However, in this study the entire PA catheterization procedure averaged 21 min in the 63 patients in whom PA was catheterized successfully. While this is longer than catheterization via IJV, the time difference is hardly important clinically considering the duration of the operative procedures and the potential for reducing the frequency of serious complications.

Systolic arterial pressure was increased significantly, in all patients in this investigation, immediately after insertion of the PA catheter. This increase was greater in group II than in the other two groups. In addition, increases in SAP began before PA catheterization in group II and were associated with significant increases in HR.

These findings are similar to those previously reported by Lunn and co-workers (1979), during catheterization of PA via IJV. They suggest that location of the skin puncture site, reflexes initiated by stimulation of tissues of the neck or position of the body or head (in Lunn's study patients were in the Trendelenberg position with the head turned away from the side of skin puncture) do not play an important role in cardiovascular stimulation during PA catheterization.

The results of this study demonstrate that percutaneous catheterization of PA via an antecubital vein (preferably the right median antecubital or basilic vein) is a simple and effective technique which eliminates many of the problems of PA catheterization via IJV. Unfortunately, increases in SAP and HR associated with PA catheterization via the arm in an unanaesthetized patient appear not to be different from those found during PA catheterization via IJV.

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CATHETERISME PERCUTANE DE L'ARTERE PULMONAIRE PAR L'INTERMEDIAIRE DU BRAS AVANT L'ANESTHESIE: TAUX DE REUSSITE, FREQUENCE DES COMPLICATIONS, ET REACTION DE LA PRESSION ARTERIELLE ET DE LA FREQUENCE CARDIAQUE

RESUME

Le taux de réussite, la fréquence des complications ainsi que les changements dans la pression artérielle systolique et la fréquence cardiaque pendant le cathétérisme percutané de l'artère pulmonaire par l'intermédiaire d'une veine antécubitale ont été estimé avant l'induction de l'anesthésie sur 84 patients prêts à subir une intervention chirurgicale cardiaque. Parmi les complications sérieuses, nous indiquerons: l'angine (2%) et une petite déchirure de la valvule tricuspidienne (un patient). Lorsqu'on a utilisé l'une des veines basiliques, le taux de réussite a été de 93%. Lorsqu'il a fallu utiliser la veine céphalique, le taux de réussite est tombé à 60%. Dans l'ensemble, le taux de réussite moyen a été de 75%. Le fait de placer le cathéter dans l'artère pulmonaire a entraîné une augmentation immédiate de la pression artérielle systolique chez tous les patients et une augmentation significative de la fréquence cardiaque chez les patients ne prenant pas d'agents de blocage béta-adrénergiques. Cette étude démontre que le cathétérisme percutané de l'artère pulmonaire par l'intermédiaire de la veine basilique est une technique simple, sûre, efficace ne comportant que peu de complications.

PERKUTANE EINFÜHRUNG EINES KATHETERS IN DEN LUNGENSCHLAGADER ÜBER DEN ARM VOR DER ANÄSTHESIE: ERFOLGSANTEIL, FREQUENZ VON KOMPLIKATIONEN UND WIRKUNG AUF ARTERIENDRUCK UND HERZSCHLÄGE PRO MINUTE

ZUSAMMENFASSUNG

Der Erfolgsanteil, die Frequenz von Komplikationen und die Änderungen des systolischen Arteriendrucks und der Herzschläge pro Minute während der perkutanen Kathetereinführung in den Lungenschlagader über eine vorulnäre Vene wurden vor Einleitung der Anästhesie bei 84 Patienten ausgewertet, die sich gerade der Herzchirurgie unterziehen sollten. Ernsthafte Komplikationen traten in der Form von Angina (2%) und einem kleinem Riss in der Trikuspidalklappe (1 Patient) auf. Als eine der venae basilicae dazu verwendet wurde, stieg der Erfolgsanteil auf 93%. Als es notwendig war, eine der venae cephalicae zu verwenden, fiel der Erfolgsanteil auf 60% zurück. Der Gesamterfolgsanteil betrug 75%. Das Einsetzen des Katheters in den Lungenschlagader führte sofort zu einer Zunahme des systolischen Arteriendrucks bei allen Patienten und zu einer bedeutenden Zunahme der Herzschläge pro Minute bei Patienten, die keine beta-adrenergische Blockierungsmittel bekamen. Diese Unterschungen zeigen, dass die perkutane Kathetereinführung in den Lungenschlagader über die vena basilica eine einfache, sichere und effektive Methode darstellt, die mit wenigen Komplikationen verbunden ist.

CATETERIZACION PERCUTANEA DE LA ARTERIA PULMONAR A TRAVES DEL BRAZO, ANTES DE LA ANESTESIA: PORCENTAJE DE EXITOS, FRECUENCIA DE COMPLICACIONES Y PRESION ARTERIAL, Y RESPUESTAS DEL RITMO CARDIACO

SUMARIO

Se evaluaron el porcentaje de éxitos, la frecuencia de las complicaciones y los cambios en la presión sistólica arterial y el ritmo cardíaco durante la cateterización percutánea de la arteria pulmonar, vía una vena anticubital, antes de inducir anestesia en 84 pacientes a punto de sometérseles a cirugía cardíaca. Las complicaciones serias fueron de angina (2%) y de una pequena ruptura en la válvula tricúspide (un paciente). Cuando se usó una de las venas basilícas, el procentaje de éxitos fue del 93%. Cuando fue necesario usar una vena cefálica, dicho régimen disminuyó hasta el 60%. El porcentaje global de éxitos fue del 75%. El colocar el catéter en la arteria pulmonar tuvo como consecuencia un incremento inmediato de la presión sistólica arterial, en todos los pacientes, y un incremento significativo del ritmo cardíaco, en aquellos pacientes que no tomaron drogas beta-adrenérgicas de bloqueo. Este estudio demuestra que la cateterización percutánea de la arteria pulmonar, vía la vena basílica, es una técnica sencilla, segura y eficaz que viene asociada con muy pocas complicaciones.

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HEPATIC DAMAGE AFTER EXPOSURE TO HALOTHANE IN MEDICAL PERSONNEL

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SUMMARY

Two surgeons, in whom liver damage developed after occupational exposure to sub-anaesthetic doses of halothane, were found to have a circulating antibody which reacted specifically with halothane-altered hepatocyte membrane components. This antibody has been found previously only in those patients in whom severe hepatic necrosis developed after exposure to halothane and in no other form of liver injury. It may provide a specific diagnostic marker in patients in whom there are other possible causes of liver damage and could, therefore, remove the need for a challenge exposure and its attendant risks.

Although massive hepatocellular necrosis after exposure to halothane is rare (Strunin, 1977), up to 20% of patients have evidence of mild hepatic damage (Trowell, Peto and Crampton-Smith, 1975; Wright et al., 1975). There have been a few reports of liver damage developing in medical and paramedical personnel after exposure to sub-anaesthetic doses of the drug (Belfrage, Ahlgren and Axelson, 1966; Klatskin and Kimberg, 1969; Johnston and Mendelsohn, 1971; Lund, Skulberg and Helle, 1974). The evidence for the association is circumstantial, based on detection of abnormal liver function tests after exposure and exclusion of other causes.

In recent studies of the mechanisms of hypersensitivity-induced liver damage, we have shown that patients in whom fulminant hepatic failure develops after multiple exposures to halothane may have a circulating antibody which reacts with a specific halothane-related hepatocyte membrane determinant (Vergani et al., 1980). We describe two medical practitioners in whom hepatic damage developed after occupational exposure to halothane and in whom the antibody was detected.

CASE REPORTS

Patient 1

An Italian surgeon aged 41 yr had been working for 15 yr in operating theatres where he was exposed to both halothane and methoxyflurane. Seven years before presentation he suffered an episode of acute hepatitis; no cause was found and he recovered completely. Six years later (May 1974), he had a further illness with features similar to hepatitis which resolved after bed-rest. Two months later, after returning to work, an increase in serum glutamic-oxaloacetic transaminase (SGOT) was noted (fig. 1). He was absent from work for 2 months during which the transaminase concentration returned to normal. He returned to work, but again felt unwell and plasma SGOT was found to be increased. He stayed away from work again. Liver biopsy showed a conspicuous mononuclear-cell infiltrate in the portal tracts but without extension to the parenchyma; there was some necrosis of single hepatocytes. This combination resembled unresolved acute hepatitis. Subsequently, after he returned to hospital duties, an increase in SGOT was noted on two occasions, both associated with halothane exposure. The patient was referred to the Liver Unit, King's College Hospital. There was no history of eczema, allergy or exposure to other known hepatotoxins or excess alcohol. On examination, there were no skin signs of chronic liver disease and no enlargement of liver or spleen. Hepatitis B surface antigen, antibody, and anticore antibody and specific immunoglobulin M (IgM) to hepatitis A virus could not be detected by radioimmunoassay and enzyme-linked immunosorbent assay. Antigastric parietal cell antibodies were present in small titres (1 in 20). Liver biopsy showed a dense but well-defined infiltration of the portal tracts by mononuclear cells which were associated with some mononuclear cells within the parenchyma.

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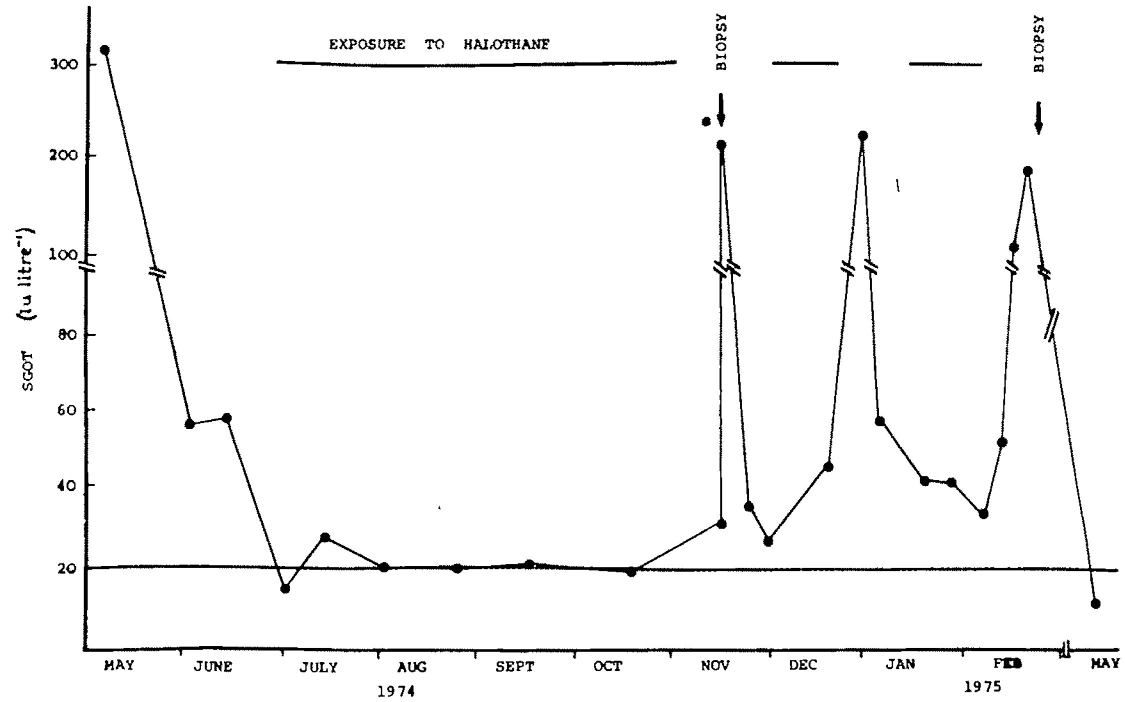

FIG. 1. Repeated episodes of "hepatitis" in relation to exposure to halothane (patient 1). Dotted line represents upper limit of normal range of SGOT.

This resembled unresolved hepatitis. The patient was advised to work only in a halothane-free environment and since then he has remained well with a normal serum transaminase concentration.

Patient 2

A Canadian doctor aged 26 yr developed a pyrexial illness with increased plasma SGOT after 3 months exposure to halothane. He returned to work but, 1 month later, was admitted to a local hospital with a 5-day history of fever, sore throat and conjunctivitis for which he was given penicillin with no effect. There was no history of exposure to hepatitis or known hepatotoxins. On examination, there was periorbital swelling and conjunctivitis, but there were no skin signs of chronic liver disease and no hepatomegaly. Plasma SGOT on admission was greater than normal (51 iu litre^{-1}) and increased the next day (90 iu litre^{-1}). There was no eosinophilia and serum autoantibodies were not detected. Tests for markers of hepatitis A and B viral infection were negative and antibody titres to Epstein Barr virus and cytomegalovirus were normal. Serum transaminases decreased gradually and were within normal limits 2 months later. Liver biopsy was not performed, at the patient's request. He changed his specialty to avoid further exposure to halothane and has remained well since.

DETECTION OF HALOTHANE- AND METHOXYFLURANE-RELATED ANTIBODIES

Target hepatocytes were isolated from female New Zealand white rabbits, exposed 18 h previously to either 1% halothane or 1% methoxyflurane and 99% oxygen (Vergani et al., 1980). Antibodies in the serum were detected both by an indirect immunofluorescence technique and a microcytotoxocity assay. Serum was heat-inactivated and absorbed with normal hepatocytes to remove any antibodies reacting with normal liver cell determinants. For immunofluorescence studies, hepatocytes were isolated by mechanical means and incubated with the patient or control serum (diluted 1 in 10) for 30 min. After three washes, the hepatocytes were incubated for a further 30 min with FITC-conjugated anti-human immunoglobulin (diluted 1 in 4). After three more washes, the cells were examined under ultraviolet microscopy.

To assay microcytotoxicity the hepatocytes were isolated by collagenase digestion and seeded into microculture test wells. Test and control serum diluted 1 in 100 were added to the wells for 2 h to allow any antibody present in the serum to react with specific determinants on the hepatocytes. After the hepatocytes were washed, lymphocytes isolated from normal individuals were added so that antibody-coated hepatocytes could be killed by a subpopulation of the lymphocytes, K cells. After 48 h, the number of viable hepatocytes was counted and the percentage cytotoxicity determined.

RESULTS

Halothane-related antibody was found in the serum of both patients by both methods. Characteristic granular fluorescence was produced by both sera with halothane-treated hepatocytes (fig. 2) and no fluorescence was seen with normal hepatocytes. In the cytotoxicity assay, both sera induced significant cytotoxicity to halothane-treated hepatocytes whereas neither did to normal hepatocytes (table I). Methoxyflurane-related antibodies were not found in the serum of patient 1 against methoxyflurane-treated hepatocytes.

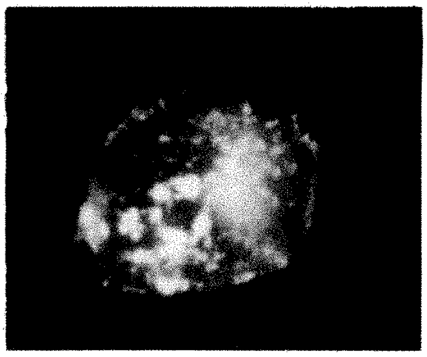

FIG. 2. Granular immunofluorescence staining pattern produced by serum of patient 2 when reacted with halothane-treated hepatocytes.

TABLE I. % *Cytotoxicity induced against treated hepatocytes by serum of patients 1 and 2. Upper limit of normal 29% (mean + 2 SD = 15 + 14). n.t. = Not tested*

	Patient	
Hepatocytes	1	2
Control	12	22
Halothane	48	38
Methoxyflurane	13	n.t.

DISCUSSION

The role of halothane-related antibody in the mechanism of the liver damage following halothane anaesthesia is not known. A direct involvement in the process of hepatic necrosis is suggested by its ability to render halothane-treated hepatocytes susceptible to lysis in the K-cell mediated antibody-dependent cytotoxicity assay *in vitro*—although *in vitro* findings cannot be equated directly with *in vivo* effects. Studies have shown the specific antibody response only in those patients in whom severe liver damage has developed after several halothane exposures and not those in whom there has been only a minimal increase in serum transaminase concentrations. Furthermore, this halothane-related antibody has not been detected in the serum of anaesthetists, exposed to halothane, who have normal liver function tests (Davis et al., 1980; Vergani et al., 1980). This is the first report of an association with a relatively minor degree of liver damage. This may be because anaesthetists are exposed to relatively small doses of the drug over a long period of time. Such occupational exposure to halothane has been shown to result in enhanced enzyme induction, as measured by antipyrine clearance (Duvaldestin et al., 1981); in susceptible individuals, this might be enough to enhance halothane biotransformation and generate the halothane-related antigen.

The increased frequency and greater severity of liver damage after multiple exposures together with unexplained postoperative pyrexia, arthralgia, eosinophilia, and circulating autoantibodies (including liver–kidney microsomal autoantibodies which are associated with hypersensitivity reactions) are all consistent with an immunologically-mediated hypersensitivity reaction (Walton et al., 1976; Strunin, 1977). The presence of the halothane-related antibody is caused by sensitization to an antigen probably resulting from covalent binding of a halothane metabolite to cellular macromolecules (Neuberger et al., 1980).

In both these patients, there was other evidence implicating halothane in the aetiology of recurrent hepatitis. On each occasion the increase in serum transaminase concentrations was closely related to exposure to halothane and the transaminases

TABLE II. *Characteristics of reported cases of medical personnel with halothane-related liver damage. n.r. = Not recorded; n.t. = not tested; *SMA = smooth muscle antibodies; GPC = gastric parietal cell antibodies*

Reference	Patient age (yr)/sex	Eczema or allergy	Eosinophilia	Autoantibodies*	Liver histology	Challenge test	Hepatitis virus excluded
Belfrage, Ahlgren and Axelson (1966)	32/M	+	+	n.r.	n.t.	+ve	n.t.
Klatskin and Kimberg (1969)	44/M	+	–	n.r.	Post-hepatitis cirrhosis	+ve	n.t.
Johnston and Mendelsohn (1971)	26/F	–	+	SMA	Hepatitis	n.t.	B
Lund, Skulberg Helle (1974)	28/F	+	n.r.	n.r.	Hepatitis	+ve	B
Present report							
1	41/M	–	–	GPC	Hepatitis	n.t.	A,B
2	26/M	–	–	–	n.t.	n.t.	A,B

returned to normal when the patient was no longer in contact with halothane. Liver histology, available in only one patient, was compatible with drug-induced liver injury (Zimmerman, 1978).

There have been reports of liver damage in medical and paramedical personnel exposed to sub-anaesthetic doses of halothane (Belfrage, Ahlgren and Axelson, 1966; Klatskin and Kimberg, 1969; Johnston and Mendelsohn, 1971; Lund, Skulberg and Helle, 1974). Hepatitis has also been reported in those who have abused halothane (Schatzki, Kay and Dickinson, 1973); Kaplan et al., 1979) although they may have been exposed to much greater doses of halothane. Of the former group, three had a history of allergy or eczema, two had peripheral eosinophilia, and one had serum autoantibodies (table II). Liver histology showed a hepatitis which progressed in one patient to cirrhosis. Other causes of liver damage, especially A and B viral hepatitis, were not always excluded.

If a patient is thought to be sensitive to halothane, it is possible to ensure that he is not exposed to it again. It is much more difficult for an anaesthetist. In practice, it may mean a change in his work. Therefore every effort should be made to determine whether or not a person is sensitized to halothane. Controlled re-exposure would put a patient already sensitized at serious risk of developing potentially fatal hepatic necrosis. Furthermore, an increase in serum transaminase concentration may indicate only that halothane is exacerbating pre-existing liver disease. By providing a specific marker of sensitization, the halothane-related antibody obviates the need for a challenge test.

ACKNOWLEDGEMENTS

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LESION HEPATIQUE APRES EXPOSITION DU PERSONNEL MEDICAL A L'HALOTHANE

RESUME

On a trouvé que deux chirurgiens souffraient d'une lésion hépatique consécutive à leur exposition professionnelle à des doses non anesthésiantes d'halothane et qu'ils avaient dans leur circulation sanguine un anticorps qui réagissait spécifiquement aux composants de la membrane d'hépatocytes modifiés par l'halothane. On n'avait précédemment trouvé cet anticorps que chez les patients sur lesquels une nécrose hépatique grave s'était développée après exposition à l'halothane, mais dans aucune autre forme de lésion du foie. Il peut constituer un facteur d'identification spécifique de diagnostic chez les patients ayant d'autres causes possibles de lésion du foie et pourrait, donc, éliminer la nécessité d'une exposition d'épreuve avec tous les risques que cela comporte.

LEBERSCHADEN BEI MEDIZINISCHEM PERSONAL NACH AUSGESETZTSEIN AN HALOTHAN

ZUSAMMENFASSUNG

Bei zwei Chirurgen, bei denen Leberschäden nach berufsbedingtem Ausgesetztsein an Subanästhesie-Dosen von Halothan auftraten, wurden kreisende Antikörper gefunden, die spezifisch mit halothanveränderten Hepatozytmembranbestandteilen reagierten. Dieser Antiköper ist bis jetzt nur bei Patienten gefunden worden, bei denen eine schwere Lebernekrose nach Ausgesetztsein an Halothan auftrat, und bei keiner anderen Form von Leberschaden. Er könnte einen spezifischen Hinweis bei Patienten geben, bei denen andere Ursachen vorliegen könnten und somit die Notwendigkeit eines herausfordernden Aussetzen und die damit verbundenen Gefahren vermeiden.

DANO HEPATICO EN EL PERSONAL MEDICO DESPUES DE SU EXPOSICION AL HALOTANO

SUMARIO

Se averiquó que dos cirujanos que habían desarrollado complicaciones en el hígado después de su exposición a dosis subanestésicas de halotano, como consecuencia de sus actividades profesionales, presentaban un anticuerpo en circulación que reaccionaba de forma específica con los componentes de la membrana hepatocítica que habían sufrido alteración a causa de dicho halotano. Este anticuerpo se había encontrado anteriormente sólo en aquellos pacientes en los que se desarrolló una necrosis hepática aguda después de su exposición al halotano, no habiéndose presentado en ningún otro tipo de complicación hepática. Puede que esto provea un indicador específico para efectuar diagnósticos en aquellos pacientes en los que, seguramente, las complicaciones hepáticas tengan otro tipo de causas y, por lo tanto, podía hacer innecesaria la exposición de prueba y sus riegos congénitos.

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BENZODIAZEPINES AS ORAL PREMEDICANTS

J. KANTO

SUMMARY

The advantages of the benzodiazepines as oral premedicants are: clear anxiolytic and sedative effect; less clear amnesic action which may prevent the recall of the time spent lying on an uncomfortable theatre trolley, but not necessarily recall of the journey to the operating theatre, or induction of anaesthesia; convenient route of administration; long duration of action of 5–8 h which simplifies timing of drug administration; adverse autonomic, hormonal and circulatory system reactions seem to be prevented, thus preventing the stress reaction even before induction of anaesthesia; anticonvulsant and muscle-relaxing actions may be of value in patients receiving local anaesthesia, or in preventing the side-effects of depolarizing muscle relaxants; nausea before and after operation may be decreased; reduced frequency of side-effects before and after operation.

Objects of premedication

The aim of premedication is to establish mental and emotional relaxation, reduce sensory input and metabolic rate and antagonize adverse reactions of the autonomic nervous system (Collins, 1976). The use of morphine before anaesthesia was suggested by Lorenzo Bruno in 1850 (Collins, 1976) and since then, narcotics have been used extensively (Collins, 1976). However, potent analgesics should only be given to patients with pain since, otherwise, a state of dysphoria may result (Cohen and Beecher, 1951; Collins, 1976). The routine use of anticholinergics has also been questioned (Mirakhur, Dundee and Connolly, 1979) especially in the elderly (Roberts, 1976).

Since 1965 there has been an increased use of oral premedicants, especially benzodiazepines (Dundee and Haslett, 1970) and it has been suggested that oral administration might be more satisfactory than i.m. (McCaughey and Dundee, 1972; Dundee, Lilburn et al., 1977; Lindgren, Saarnivaara and Himberg, 1980). The high frequency of venous sequelae after i.v. administration favours the oral route of administration (Dundee, 1979). Benzodiazepines are useful premedicants since they can reduce apprehension, excitement and autonomic nervous system reactions before anaesthesia and surgery (Dundee and Haslett, 1970).

The preoperative visit by the anaesthetist has been shown to reduce anxiety (Leigh, Walker and Janaganathan, 1977), but for optimum effect the visit should be combined with medication (Norris and Baird, 1967). Psychological benefits may last up to 18 h after the visit (Egbert et al., 1963) and the anaesthetist should not underestimate the value of this procedure (Eckenhoff and Helrich, 1958). No reduction in anxiety was found when the sole addition to atropine was a barbiturate (Cohen and Beecher, 1951; Eckenhoff and Helrich, 1958). It has even been stated by patients that anaesthetists are clever doctors who lack emotional impact (Sheffer and Greifenstein, 1960).

Since potent induction agents are now available the primary aims of premedication and the preoperative visit are to reduce patient's fears and to prevent stress reactions beginning even before induction of anaesthesia. The use of benzodiazepine derivatives as oral premedicants is reviewed here with special reference to their antianxiety property.

Oral v. other routes of administration

At physiological pH, all benzodiazepines are highly lipid-soluble and fairly rapidly and almost completely absorbed after oral ingestion (Bellantuono et al., 1980). After i.m. injection, absorption of diazepam (Kanto, 1975) and chlordiazepoxide (Greenblatt, Shader et al., 1978) is slow and erratic, possibly because of crystallization at the injection site. In contrast, lorazepam (Elliot, 1976), flunitrazepam (Clarke et al., 1980), and chlorazepate (Rey et al., 1979) are absorbed more rapidly following i.m. than after oral administration. Following i.v. injection, a rapid and

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reliable sedative effect has been found after diazepam, chlordiazepoxide and flunitrazepam, but subjects to whom lorazepam was given orally appeared to be as sedated as those to whom it had been administered i.m. or i.v. (Elliot, 1976). The reason for the slow onset of action of lorazepam appears to be its slow penetration of the blood–brain barrier (Aaltonen, Kanto and Salo, 1980) and similarly, its placental transfer is retarded compared with diazepam (Kanto, Aaltonen et al., 1980).

After i.m. injection, prolonged pain at the injection site has been reported for each compound, sometimes lasting weeks (Kanto, 1975; Greenblatt, Shader et al., 1978a; Dundee et al., 1979; Clarke et al., 1980). Local sequelae following i.v. injection were less with flunitrazepam than with diazepam (Hegarty and Dundee, 1978). Both these side-effects support the oral use of benzodiazepines as premedicants. Rectal administration of diazepam in solution is reliable, but suppositories result in variable plasma concentrations (Kanto, 1975; Knudsen, 1977).

Interactions

Antacids reduce the rate (diazepam and chlordiazepoxide) or both the rate and amount (nordiazepam from chlorazepate) of benzodiazepines reaching the systemic circulation (Greenblatt, Shader et al., 1978; Greenblatt, Allen et al., 1978; Bellantuono et al., 1980). However, this effect on the absorption of diazepam seems to depend on the nature of the antacid (Nair et al., 1976).

The addition of morphine, pethidine or atropine to oral diazepam premedication resulted in slower gastrointestinal absorption, while the addition of metoclopramide increased the rate of absorption and resulted in greater plasma diazepam concentrations (Gamble et al., 1976). Oral administration of ethanol and diazepam was associated with greater plasma diazepam concentrations and a smaller volume of distribution than after diazepam alone and the pharmacological effects of diazepam were potentiated (MacLeod et al., 1977). Cimetidine also potentiated the sedative effect of diazepam (Klotz and Reimann, 1980), while disulfiram decreased the clearance of diazepam and chlordiazepoxide, but not that of oxazepam (MacLeod et al., 1978).

In general, all benzodiazepines increase the central depressant effect of other sedatives, hypnotics, antipsychotic drugs and tricyclic antidepressants, especially at the start of treatment (Burrows, 1976).

Effect of age and disease

In full-term and, especially, in premature infants, capacity for metabolizing benzodiazepines is limited and long-lasting sequelae are possible (Morselli, 1976; Kanto, 1980). Similarly, an increased frequency of side-effects has been reported in the elderly (Bellantuono et al., 1980).

Oxazepam and lorazepam do not need oxidative metabolism before glucuronidation and there may be no change in their distribution and elimination with increasing age or in disease (Shull et al., 1976; Verbeeck et al., 1976; Odar-Cederlöf et al., 1977; Kraus et al., 1978; MacLeod et al., 1978). In contrast, both age and disease cause marked changes in the pharmacokinetics of diazepam, chlordiazepoxide, nitrazepam and chlorazepate (Klotz et al., 1975; Kangas et al., 1976, 1979; Greenblatt, Shader et al., 1978; Kanto, Mäenpää et al., 1979; Klotz and Müller-Seydlitz, 1979; Ochs et al., 1979) resulting in an increased drug effect. In addition to kinetic changes, there is apparently an increased sensitivity to sedatives in old age and benzodiazepines should be used in reduced doses (Bellantuono et al., 1980).

Curiously, the rate of absorption of diazepam from the gastrointestinal tract has been found to be faster in subjects with a high neuroticism score than in those with a low score (Nakano, Ogawa and Kawazu, 1980). This may have clinical significance because the rapidity of increase in concentration, rather than the absolute value, seems to determine the subjective drug effect of the benzodiazepines (Bliding, 1974).

Anxiolysis

Anaesthesia and surgery constitute great psychic stress in any patient. The effectiveness of drugs given before operation on this transient anxiety and on autonomic nervous system reactions can be evaluated and compared, because the primary goal is to free the patient from fear, restlessness and autonomic reactions (Forrest, Brown and Brown, 1977; Kanto, Kangas and Mansikka, 1979). The overall frequency of anxiety before anaesthesia is 40–60% (Norris and Baird, 1967). Using an extensive psychological questionnaire, as many as 80% of patients were anxious (Corman et al., 1958). A greater frequency has been found in females than in males, in females less than 70 kg more often than in females over this weight and in patients receiving sedative drug therapy (Norris and Baird, 1967). In orthopaedic patients, anxiety remained greater for several days after surgery, but women undergoing elective gynaecological operations were more anxious on the day before admission to hospital than on the day before surgery (Johnston, 1980). Thus, in selected cases, the anxiety-relieving efforts should last longer than is generally the case.

A positive correlation between anxiolysis and ease of induction of anaesthesia has been reported (Lindgren, Saarnivaara and Himberg, 1980), which supports the importance of the anxiolytic component of premedication. Relief of apprehension may reduce excessive hormonal and circulatory response to anaesthesia and may reduce the minimum effective dose of anaesthetic agents (Male et al., 1980).

In comparison with placebo or no premedication, oral flunitrazepam 1–2 mg (Kanto, Kangas and Mansikka, 1979; Male et al., 1980), nitrazepam 5 mg (Kangas, Kanto and Mansikka, 1977), lorazepam 2.5–5 mg (Male et al., 1980) and chlordiazepoxide 25–50 mg (Brandt, Lui and Briggs, 1962) have produced significantly greater anxiolysis. Oral medazepam 10 mg (Assaf, Dundee and Bali, 1975; Herbert, Bourke and Rose, 1979), diazepam 10–20 mg (Assaf, Dundee and Bali, 1975; Male et al., 1980) and oxazepam 30 mg (Mansikka et al., 1979) have failed to alleviate fear in some studies. The high placebo response resulting from frequent visits to patients has been thought to affect these results (Assaf, Dundee and Bali, 1975). However, in patients undergoing conservative dentistry, medazepam was effective in allaying apprehension (Hailey and Baird, 1979).

Better anxiolysis can be induced in children aged less than 5 yr with drugs other than benzodiazepines such as trimeprazine or triclofos. However, in older children benzodiazepines are useful (Haq and Dundee, 1968; Boyd and Manford, 1973; Lindgren, Saarnivaara and Himberg, 1980) and better than oral premedicants such as phenobarbitone and trimeprazine (Gordon and Turner, 1969). In anxious children, the significance of preoperative crying and tachycardia in increasing bleeding after adenotonsillectomy has been established (Haq and Dundee, 1968). In contrast, it has been reported that the behaviour of unsedated children in the anaesthetic room was comparable to that of children given sedative premedication. Therefore, unsedated children should be included in premedication studies (Beeby and Hughes, 1980).

The anxiolytic effect of oral diazepam 10 mg was comparable to that of oxazepam 30 mg (Kanto, Iisalo et al., 1979), lorazepam 2 mg (Paymaster, 1973) and pentobarbitone 100 mg (Hovi-Viander, Kangas and Kanto, 1980) and there were no great differences in the effects of these agents as oral premedicants. Similarly, there was no difference between diazepam 5 mg and pentobarbitone 60 mg as rectal premedicants in small children (Kanto, Iisalo et al., 1980). However, in another study, both oral lorazepam 3 mg and diazepam 10 mg caused significantly fewer preoperative side-effects than heptabarbitone 400 mg (Wilson and Ellis, 1973). Generally, the anxiolytic property of benzodiazepines has been considered to be superior to that of barbiturates (Zimmermann-Tansella, Tansella and Lader, 1979).

We found no difference in anxiolytic response between flunitrazepam 2 mg and lorazepam 2.5 mg (Mansikka, Kangas and Kanto, 1980) and flunitrazepam 1 mg and oxazepam 30 mg (Pakkanen, Kangas and Kanto, 1981). In contrast, the frequency of restlessness and apprehension has been found to be less with flunitrazepam 1–2 mg than with lorazepam 2.5–5 mg or fosazepam 40, 60 or 80 mg (Dundee, Johnston et al., 1977). The author's opinion is that the clinically important property of flunitrazepam is its anxiolytic effect (Kanto, Kangas and Mansikka, 1979). Similarly, in a placebo-controlled study we found tofizopam to be a highly anxiolytic agent, but there was no significant difference between nitrazepam and placebo (Pakkanen et al., 1980).

In general, oral benzodiazepines seem to be effective in reducing anxiety before anaesthesia and surgery. This is important because less anxiety means safer surgery (Johnston, 1980).

Sedation

Sedation is by no means synonymous with lack of anxiety. However, it has been considered a useful property of premedicant drugs (Collins, 1976). Generally, it is easy to differentiate the sedative effect of the oral benzodiazepines from that of placebo (Assaf, Dundee and Bali, 1975; Kanto, Kangas and Mansikka, 1979; Mansikka et al., 1979; Male et al., 1980; Pakkanen et al., 1980).

In an uncontrolled study, chlordiazepoxide 50 mg orally alleviated apprehension effectively and caused evident sedation without alteration in arterial pressure or respiration. A dose of 25 mg was less good (Coppolino and Wallace, 1961). As a sedative, diazepam 10 mg is equivalent to lorazepam 2–2.5 mg (Paymaster, 1973; Dundee et al., 1979) or 3 mg (Wilson and Ellis, 1973) and to 30 mg of oxazepam (Kanto, Iisalo et al., 1979). It is, however, superior to 10 mg of medazepam (Assaf, Dundee and Bali, 1975). Similarly, diazepam 10 mg and lorazepam 3 mg were comparable to pentobarbitone 100 mg (Hovi-Viander, Kangas and Kanto, 1980) and heptabarbitone 400 mg (Wilson and Ellis, 1973). In children, diazepam 5 mg was as sedative as oxazepam 15 mg (Kanto, Iisalo et al., 1979).

Nitrazepam 5 mg caused markedly more sedation than placebo, but there was no difference between tofizopam 100 mg and placebo in this respect (Pakkanen et al., 1980). The degree of sedation obtained after two different doses of nitrazepam (5 and 10 mg) was comparable to that after one tablet of Mandrax (methaqualone 250 mg + diphenhydramine 25 mg) but postoperative emetic sequelae were greater with the larger dose of nitrazepam in comparison with the two other premedicants (Norris and Telfer, 1969).

Oral lorazepam 2 mg was comparable to nitrazepam 5 mg, while lorazepam 4 mg was similar to nitrazepam 10 mg (Norris and Wallace, 1971). Lorazepam 2 and 4 mg, while showing an increase in sedative effect with increasing dose, did not show a significant difference in comparison with one tablet of Mandrax. Similarly, doubling the dose of diazepam (from 10 to 20 mg) lorazepam (from 2.5 to 5 mg) and flunitrazepam (from 1 to 2 mg) increased the sedative effect to some extent, but failed to relieve apprehension any further (Male et al., 1980).

TABLE I. *The quality of sleep the night before operation based upon subjective assessment by patients. n.s. = not significant*

Pakkanen, Kangas and Kanto, 1980:				
Flunitrazepam 1 mg		n.s.		Oxazepam 30 mg
good 79%				89%
fair 18%				9%
poor 3%				2%
Mansikka, Kangas and Kanto, 1980:				
Flunitrazepam 2 mg		n.s.		Lorazepam 2.5 mg
good 84%				84%
fair 8%				14%
poor 8%				2%
Kanto, Kangas and Mansikka, 1979:				
Flunitrazepam 2 mg		$P<0.001$		Placebo
good 93%				22%
fair 5%				24%
poor 2%				54%
Kangas, Kanto and Mansikka, 1977:				
Nitrazepam 5 mg		$P<0.05$		No drug
good 74%				50%
fair 20%				35%
poor 6%				15%
Pakkanen and others, 1980:				
Tofizopam 100 mg	$P<0.01$	Nitrazepam 5 mg	$P<0.01$	Placebo
good 36%		74%		38%
fair 36%		18%		36%
poor 28%		8%		26%
Mansikka and others, 1979:				
Oxazepam 25 mg		$P<0.05$		Placebo
good 84%				50%
fair 16%				30%
poor 0%				20%

Flunitrazepam 1 mg had a greater sedative effect than oxazepam 30 mg (Pakkanen, Kangas and Kanto, 1981), and flunitrazepam 2 mg differed similarly from lorazepam 2.5 mg (Mansikka, Kangas and Kanto, 1980). Flunitrazepam 1 and 1.5 mg produced significantly better sedation than diazepam 10 mg or lorazepam 2.5 mg (McGowan et al., 1980). Oral flunitrazepam 1 mg has been shown, in particular, to offer advantages over placebo, diazepam 10 mg and lorazepam 2.5 mg for routine premedication (Male et al., 1980). In children, oral flunitrazepam 1, 1.5, and 2 mg, was associated with greater preoperative sedation than oral diazepam 10, 15, and 20 mg (Richardson and Manford, 1979).

The sedative effect of the benzodiazepine derivatives as oral premedicants seems to be clinically comparable to that of drugs which have been in use longer, such as barbiturates, antihistamines and chloral derivatives. Our results on the quality of sleep on the night before operation are presented in table I.

Amnesia

The benzodiazepines have a specific amnesia-producing property especially when administered i.v. (George and Dundee, 1977). Amnesia for unpleasant aspects of the perioperative period is a useful property of premedication, but lack of recall of picture cards or other such items does not necessarily mean that the patient will not remember such events as journey to the operating theatre or induction of anaesthesia.

The amnesic action of oral diazepam 10 mg has been assessed as superior to that of placebo (McKay, Dundee and George, 1978), similar to that of heptabarbitone (Wilson and Ellis, 1973) and inferior to that of trimeprazine (Haq and Dundee, 1968). The more potent soporific effect of trimeprazine may explain this difference although the anterograde amnesic action of benzodiazepines is not wholly dependent on sedation. However, significant failure to identify cards seems to require appreciable sedation at the time of card presentation (Dundee et al., 1979).

The amnesic action of oral diazepam 10 and 20 mg is dose-dependent: after 10 mg, amnesia lasts for 120 min (i.v. route 15–20 min) while after 20 mg as many as 50% of patients had poor recall of events during the day of operation (Brandt and Oakes, 1965; Baird and Hailey, 1972). In contrast, Harry and Richards (1971) showed a negligible difference between diazepam 10 and 20 mg and that neither dose was as potent as oral lorazepam 2 or 4 mg.

Lorazepam is capable of producing dose-dependent, prolonged amnesia with slower onset of action than other benzodiazepines (George and Dundee, 1977). A 1-mg oral dose does not appear to affect memory (Dundee et al., 1979) while increasing the oral dose from 4 to 5 mg does not increase the frequency of anterograde amnesia (Dundee, Lilburn et al., 1977). Almost half the patients receiving lorazepam 4 mg had complete amnesia for events occurring 60–90 min after drug administration irrespective of the route of administration (p.o., i.m.; Dundee, Lilburn et al., 1977). In general, lorazepam has been considered to be the most potent benzodiazepine derivative in causing long-lasting (up to 8 h or more) amnesia which is pleasant for patients (Wilson and Ellis, 1973; George and Dundee, 1977; Dundee, Lilburn et al., 1977). However, the slow onset of action of lorazepam must be taken into consideration when timing premedication. It is an effective oral premedicant when rapid recovery is not essential (Dundee, Lilburn et al., 1977). In contrast to diazepam and flunitrazepam, its amnesic action is paralleled by its sedative effect (George and Dundee, 1977).

The relative amnesic action and duration of effect of flunitrazepam seem to be greater than those of diazepam (George and Dundee, 1977a). A dose-dependent effect was found 1 h after premedication when the amnesic property of diazepam 10 and 20 mg, lorazepam 2.5 and 5 mg, flunitrazepam 1 and 2 mg, and placebo were compared. The results were almost similar with flunitrazepam and lorazepam and superior to those with diazepam (Male et al., 1980). In children also, oral flunitrazepam 1, 1.5, and 2 mg caused a greater frequency of amnesia than oral diazepam 10, 15, and 20 mg (Richarson and Manford, 1979).

The amnesic actions of lorazepam and flunitrazepam seem to be superior to that of diazepam. Oral premedication with lorazepam, in particular, provides significant anterograde amnesia with good sedation and some postoperative basal narcosis (Wilson, 1973).

Other actions

In the doses used for oral premedication, benzodiazepines appear to have little effect on the cardiovascular or respiratory systems. They are less likely to cause postoperative nausea and vomiting than are the strong analgesics and their effect seems to be at least as good as that of opiates, with fewer side-effects (Norris and Telfer, 1969; Wilson, 1973). Oral flunitrazepam and nitrazepam significantly decreased heart rate in comparison with placebo or no premedication (Kangas, Kanto and Mansikka, 1977; Kanto, Kangas and Mansikka, 1979) and flunitrazepam prevented increase in systolic arterial pressure more effectively than oxazepam (Pakkanen, Kangas and Kanto, 1981). Furthermore, flunitrazepam was associated with less postoperative vomiting than diazepam (Richardson and Manford, 1979). The antiemetic action of benzodiazepines has, however, not been proved in all studies (Kangas, Kanto and Mansikka, 1977; Kanto, Kangas and Mansikka, 1979; Mansikka et al., 1979; Pakkanen et al., 1980). In addition, the antisialagogue effect of the benzodiazepines is poor, especially in children (Haq and Dundee, 1968; Boyd and Manford, 1973; Lindgren, Saarnivaara and Himberg, 1980) and in patients undergoing e.n.t. procedures (Pakkanen, Kangas and Kanto, 1981).

Theoretically, the anti-convulsant and muscle-relaxing actions of benzodiazepines could be of value in patients receiving local anaesthesia, but the clinical significance of this is unknown (Wesseling, 1973). Prolonged neuromuscular blockade in conjunction with tubocurarine has been observed (Feldman and Crawley, 1970a, b) but, again, the clinical significance of this observation remains to be elucidated. In children, flunitrazepam has been shown to prevent fasciculations caused by suxamethonium more effectively than diazepam or triclofos (Lindgren, Saarnivaara and Himberg, 1980). Lorazepam has caused a relatively high frequency (9%) of adverse reactions in some studies (Mansikka, Kangas and Kanto, 1980) apparently caused by marked muscle relaxation.

The benzodiazepines have no analgesic action, but mothers receiving them during labour appear to require smaller doses of analgesics (Dundee, 1979; Kanto, 1981).

Following nitrazepam (Kangas, Kanto and Mansikka, 1977) and diazepam (Paymaster, 1973) premedication, an increased frequency of headache has been recorded but, in contrast, flunitrazepam seems to protect from this sensation (Kanto, Kangas and Mansikka, 1979). The benzodiazepines often cause dizziness (Paymaster, 1973; Kanto, Kangas and Mansikka, 1979; Clarke et al., 1980). Lorazepam 4 mg orally has been shown to prevent central sequelae after ketamine more effectively than other compounds, which has made ketamine acceptable to patients as an induction agent (Dundee et al., 1979).

The insertion of an i.v. cannula has been significantly more difficult after placebo premedication compared with oxazepam (Mansikka et al., 1979). The difference also almost reached significance between flunitrazepam and placebo (Kanto, Kangas and Mansikka, 1979). However, in neither study did the temperature of the forefinger before, during or after the anaesthesia vary significantly between the two groups. Measurement of cutaneous temperature of the finger as an indication of sympathetic reaction to anaesthesia and surgery therefore seems of little use.

A large oral dose of nitrazepam (40 mg) as a premedicant has been shown to decrease plasma cortisol concentrations compared with control (James and Fisher, 1970).

Nitrazepam decreased the induction dose of thiopentone which indicates its marked sedative effect, but tofizopam did not do so (Pakkanen et al., 1980). The benzodiazepines have provided adequate preoperative sedation over a period of 5–8 h with minimum side-effects before or after operation (fig. 1) (Norris and Wallace, 1971; Wilson and Ellis, 1973; Kanto, Kangas and Mansikka, 1979; Dundee et al., 1979). However, after nitrazepam (Bond and Lader, 1972), flunitrazepam (Bond and Lader, 1975) and flurazepam (Bond and Lader, 1973) easily detectable residual effects have been determined the day after drug administration. For inpatients this may be desirable but not, of course, in the outpatient. The author's personal view of the difference between benzodiazepine derivatives as oral premedicants is shown in table II.

Relationship between plasma concentration and effect

When used as oral premedicants, no obvious relationship has been found between the plasma concentrations and clinical effects of diazepam (Kanto, Iisalo et al., 1979; Richardson and Manford, 1979; Hovi-Viander, Kangas and Kanto, 1980), oxazepam (Kanto, Iisalo et al., 1979; Mansikka et al., 1979), nitrazepam (Kangas, Kanto and Mansikka, 1977) or flunitrazepam (Kanto, Kangas and Mansikka, 1979; Richardson and Manford, 1979). It would appear, therefore, that a

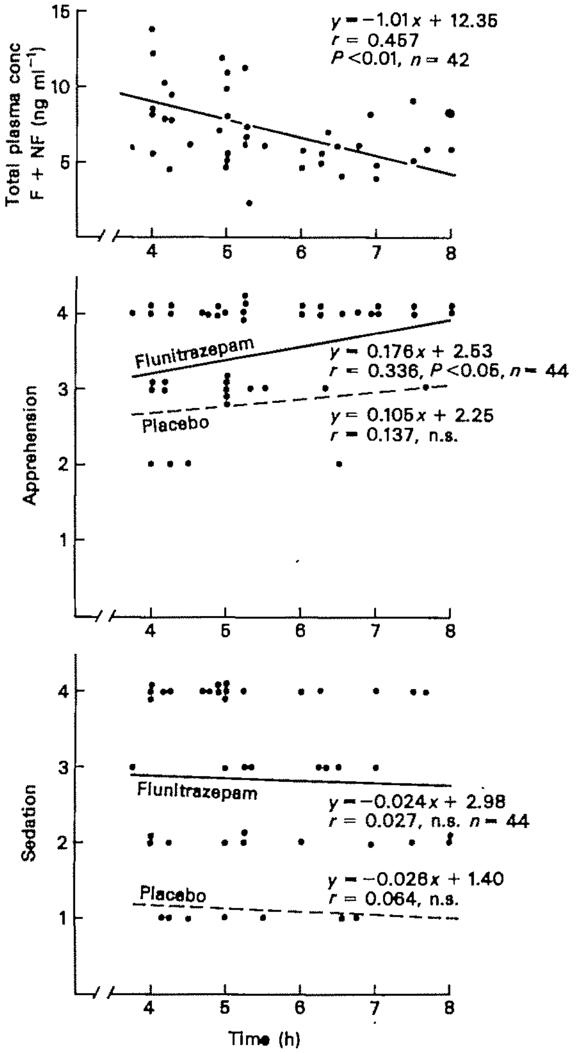

FIG. 1. Total concentration of flunitrazepam (F)+its N-demethylated metabolite (NF) in plasma after the second 2-mg oral morning dose of flunitrazepam. No correlation between the plasma concentration and clinical effect was found. Mean apprehension decreased (increase in points scored) although mean sedation remained unaltered in the flunitrazepam group (individual results + mean score). In the placebo group (mean score only), no significant change was found in apprehension or sedation during the study. The beneficial effects of flunitrazepam lasted for at least up to 8 h after the second dose (Kanto, Kanagas and Mansikka, 1979).

TABLE II. *The author's personal view of the differences between benzodiazepine derivatives estimated in the operating theatre just before induction of anaesthesia. Assessments were made after two oral doses (the night before, and morning of, operation) using the method of Dundee, Moore and Nicholl (1962), with minor alterations (diazepam 10+10 mg, nitrazepam 5+5 mg, flunitrazepam 1+1 mg or 2+2 mg, oxazepam 25+25 mg or 30+30 mg, lorazepam 2.5+2.5 mg, tofizopam 100+100 mg)*

Sedation
Flunitrazepam > lorazepam = oxazepam = diazepam = nitrazepam > tofizopam = placebo

Apprehension + excitement (anxiolysis)
Flunitrazepam = (?) tofizopam ≫ placebo < diazepam = oxazepam = lorazepam = nitrazepam

Dizziness
Flunitrazepam ≫ placebo = tofizopam ≪ nitrazepam = lorazepam > oxazepam = diazepam

Headache
Nitrazepam > placebo = diazepam = oxazepam = lorazepam = tofizopam > flunitrazepam

Cardiovascular changes
Flunitrazepam < placebo = diazepam = oxazepam = nitrazepam = lorazepam = tofizopam
Nitrazepam < no premedication

single plasma concentration value of any benzodiazepine derivative is of limited value in predicting the clinical effect of these drugs. This has been a general observation during benzodiazepine treatment (Bellantuono et al., 1980). However, in both diazepam- and flunitrazepam-treated children, plasma concentrations were significantly greater in those with amnesia for the induction period. Similarly, there was a tendency to greater benzodiazepine concentrations in those children who did not vomit after operation (Richardson and Manford, 1979).

The serum concentrations of both diazepam and flunitrazepam have been observed to be less in children of less than 5 yr than in older children, indicating age-dependent pharmacokinetics in childhood (Lindgren, Saarnivaara and Himberg, 1980).

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LES BENZODIAZEPINES ADMINISTRES EN TANT QUE MEDICATIONS PREOPERATOIRES BUCCALES

RESUME

Les avantages que présentent les benzodiazépines en tant que médications préopératoires administrées par voie buccale sont: effet nettement anxiolytique et sédatif; action amnésique moins nette qui peut empêcher de se souvenir du temps passé sur un chariot inconfortable de salle d'operations, mais pas nécessairement du temps de transport jusqu'à la salle d'opération, ou de l'induction de l'anesthésie; voie d'administration pratique; longue durée d'action—entre 5 h et 8 h—ce qui simlifie le calcul du temps pour l'administration de la médication; les réactions adverses des systèmes autonome, hormonaux et circulatoires semblent pouvoir être évitées, empêchant ainsi la réaction au stress même avant l'induction de l'anesthésie; les actions anticonvulsives et de relaxation musculaire peuvent être bénéfiques pour les malades recevant une anesthésie locale ou pour éviter les effets secondaires des agents de relaxation musculaire dépolarisants; les nausées avant et après l'intervention peuvent être diminuées; une fréquence réduite des effets secondaires avant et après l'intervention chirurgicale.

DIE ANWENDUNG VON BENZODIAZEPINEN ALS PERORALE PRÄMEDIKATION

ZUSAMMENFASSUNG

Die Vorteile der Anwendung von Benzodiazepinen als perorale Prämedikation sind wie folgt: klare angstvermindernde und beruhigende Wirkung; weniger klare amnesische Wirkung, die veilleicht ausreicht, um die Erinnerung an die Zeit zu unterdrücken, die der Patient auf dem unbequemen Rollwagen verbracht hat, aber nicht unbedingt die Erinnerung an den Gang zum Operationsraum oder an die Induktion der Anästhesie; günstige Verabreichungsweise; lange Wirkungsdauer (5–8 stunden), die die Entscheidung über den Zeitpunkt der Verabreichung vereinfacht; Nachteilige autonome, hormonale und kreislaufbezogene Reaktionen werden anscheinend vermieden, sodass die Stress-Reaktion schon vor Induktion der Anästhesie vermieden wird; krampfbekämpfende und muskelentspannende Aktivität könnte bei Patienten von Nutzen sein, die Lokalanästhesie bekommen, oder zur Vermeidung von den Seiteneffekten von depolarisierenden Muskelentspannungs mitteln; Übelkeit vor und nach der Operation könnte abnehmen: Frequenz der Seiteneffekte vor und nach der Operation reduziert ist.

BENSODIACEPINAS CUAL PREMEDICAMENTOS ORALES

SUMARIO

Las ventajas de las benzodiacepinas cual premedicamentos orales son: claros efectos de ansiedad y sosiego; una actividad amnésica menos clara que puede impedir que se recuerde el tiempo que se estuvo tendido en un imcómodo carrillo de teatro de operaciones, pero sin siempre impedir que se recuerde el viaje hasta dicho teatro de operaciones ni la inducción de la anestesia; una ruta de administración conveniente; una actividad de gran duración, de 5 a 8 h, lo que simplifica la temporización de la administración de la droga; parece que se impiden las reacciones adversas del sistema circulatorio, hormonal y autonómico, impidiendo así la tensión incluso antes de la inducción de la anestesia; puede que las actividades de relajación muscular y anticonvulsionantes sean de algún valor en aquellos pacientes que reciben anestesia local o para prevenir los efectos secundarios de los relajantes despolarizadores de músculos; las náuseas anteriores y posteriores a la operación pueden disminuirse; frecuencia disminuida de los efectos secundarios antes y después de la operación.

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INFLUENCE OF AGE AND SEX ON THE PHARMACOKINETICS OF THIOPENTONE

J. H. CHRISTENSEN, F. ANDREASEN AND J. A. JANSEN

SUMMARY

Thiopentone was given to eight women and eight men (60–79 yr). The disappearance of thiopentone from the venous blood was described by a three-compartment open model. The only significant difference between the sexes was a higher initial venous concentration in males. The dose (mg kg^{-1}) for induction was 70% of the value ($P < 0.05$) previously reported for a comparable group of younger men and women (20–40 yr). The volumes of distribution V_2 and V_3 were larger in the elderly ($P < 0.05$). The terminal half-lives were increased with advancing age (from 75% to 100% on average) ($P \leqslant 0.01$). The clearance value was 50% greater in the older women than in a group of young women. For all groups a significant correlation between initial drug concentration and k_{12} supported the hypothesis that the redistribution rate constant k_{12} is the predominant factor in the pharmacokinetic profile of a dose of thiopentone sufficient to obtund the eyelash reflex.

The dose of thiopentone required to induce anaesthesia depends on the age and the sex of the patient, Dundee (1954) and Christensen and Andreasen (1978) demonstrating that anaesthesia was induced with smaller doses in the elderly. The average induction dose (mg kg^{-1}) was significantly less in women than in men when all age groups were considered but no significant differences were present when groups of different sex but similar ages were compared (Christensen and Andreasen, 1978). Recently, the pharmacokinetics of thiopentone were compared in young men and women after the administration of the dose required to induce anaesthesia (Christensen, Andreasen and Jansen, 1980). A larger V_3 and a longer $T_{\frac{1}{2}}^{\beta}$ were noted in the women. The results suggested that the rate constant k_{12}, rather than the initial volume of distribution, was the determinant of the dose necessary to obtund the eyelash reflex.

The pharmacokinetics of thiopentone in the elderly have not been described. The present study allowed comparison of the findings with the results obtained in our previous study (Christensen, Andreasen and Jansen, 1980). The objectives were: (1) to compare groups of elderly men and women with respect to dose and pharmacokinetics; (2) to establish a basis for the comparison of four groups: young women, young men, elderly women and elderly men.

PATIENTS AND METHODS

Eight female and eight male patients gave informed consent to the study. The age range was 60–79 yr. The women underwent minor gynaecological operations, the men orthopaedic procedures. The diseases were not of an acute nature and no patients had evidence of a disease other than that for which surgery was indicated.

Pethidine 0.8 mg kg^{-1} and atropine 0.5 mg were given i.m. 30–60 min before the induction of anaesthesia. The thiopentone solution (Leopental, 2.5%) was injected to a vein on the back of the hand until the eyelash reflex was obtunded. The first 200 mg was given over 25 s. After that repeated doses of 50 mg were injected over 2 s every 20 s. Before each injection the patient was examined to determine the presence or absence of the eyelash reflex. Suxamethonium 100 mg was given to facilitate tracheal intubation and anaesthesia was maintained with halothane in nitrous oxide in oxygen. The lungs were ventilated artificially and every anaesthetic was administered by the same anaesthetist (J. H. C.).

Blood samples for the determination of thiopentone were withdrawn from an indwelling catheter inserted to a large cubital vein in the arm opposite that used for the injection. A control

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sample was taken before induction. The first sample was drawn 40 s after the last injection of thiopentone. Further samples were taken at 5, 15, 30, 45, 60 and 90 min and 2, 3, 4, 6, 8, 12, 22–24 h. The blood was allowed to coagulate, serum was obtained by centrifugation and kept refrigerated for a few days until it was analysed.

Thiopentone was analysed by high performance liquid chromatography (Christensen and Andreasen, 1979). The sensitivity of the method was 0.05 $\mu g\,ml^{-1}$.

Calculation of pharmacokinetic data

A three-compartment open model with elimination from the central compartment only was used to describe the disappearance of thiopentone from the serum. The model has been described in detail previously (Christensen, Andreasen and Jansen, 1980). The symbols for the compartmental model are in accordance with the guidelines suggested in this Journal (Editorial, 1979).

Statistical calculations

The statistical significance of observed differences was tested by the Mann–Whitney test. Correlations were tested by standard t statistics.

RESULTS

The average doses necessary for the induction of anaesthesia are listed in table I. The men required a greater dose than the women but in relation to body weight the doses were equal. On the other hand, the concentration in the peripheral venous blood was significantly greater in the male patients. For all 16 patients there was a correlation between the dose in mg per kg body weight and the initial venous concentration ($P < 0.05$).

The relationship between venous serum concentration and time is shown in figure 1 for one female and one male patient. A three-compartment open model with elimination from the central compartment only can describe both curves and the same was true for the other 14 patients. The pharmacokinetic parameters are shown in table II (women) and in table III (men). The volumes of distribution, the rate constants, the half-lives and the clearances showed no significant differences in the two groups.

TABLE I. *The induction dose of thiopentone (mg and mg per kg body weight) and the initial venous concentration in eight elderly women and in eight elderly men (mean ± SD)*

	Women	Men	P
Induction dose (mg)	231 ± 25.8	312 ± 44.3	< 0.001
($mg\,kg^{-1}$)	3.90 ± 0.68	3.97 ± 0.76	n.s.
Venous concn ($\mu g\,ml^{-1}$)	19.2 ± 6.5	34.3 ± 18.4	< 0.01

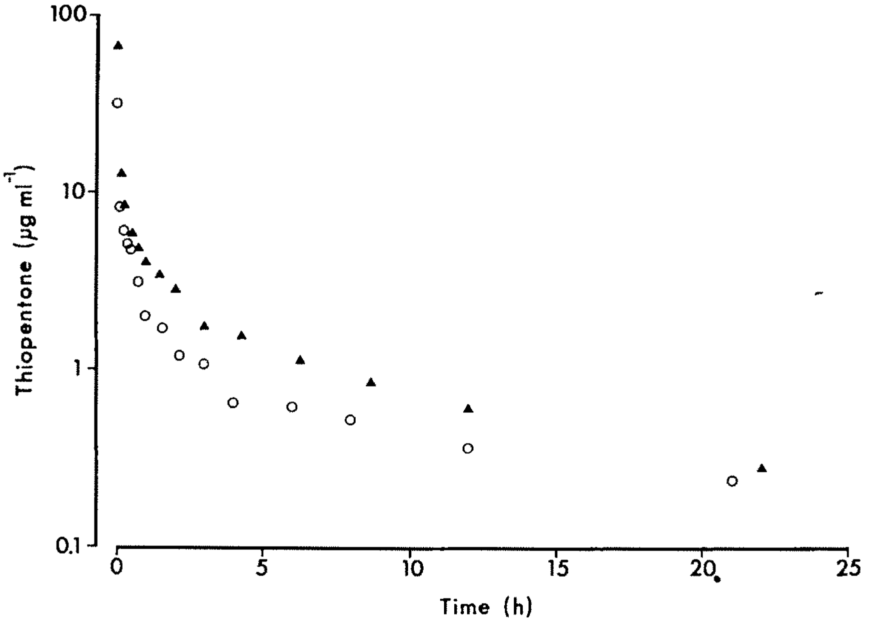

FIG. 1. The serum concentration of thiopentone as a function of time for patient ○ in table II and for patient ▲ in table III.

TABLE II. *Pharmacokinetic parameters of thiopentone in eight elderly women. The data are calculated from the concentrations in venous blood after i.v. administration within 2 min of an induction dose (250–400 mg)*

Patient	Weight (kg)	V_1 (litre)	V_2 (litre)	V_3 (litre)	k_{12} (min^{-1})	k_{13} (min^{-1})	k_{10} (min^{-1})	$T_{\frac{1}{2}}^{\pi}$ (min)	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)	Cl (litre min^{-1})
□	72	19.9	15.6	111.5	0.031	0.015	0.0085	8.3	54	813	0.168
■	66	18.4	36.4	337.2	0.055	0.028	0.0081	6.3	69	2223	0.149
○	61	4.5	19.0	112.4	0.540	0.085	0.0481	8.9	29	616	0.216
●	54	7.7	10.6	83.3	0.099	0.042	0.0179	3.3	30	668	0.137
△	47	16.9	19.0	91.7	0.043	0.015	0.0113	7.0	58	662	0.192
▲	63	10.3	20.0	213.7	0.117	0.054	0.0261	2.9	32	875	0.269
▽	58	8.5	20.1	132.6	0.210	0.047	0.0262	2.0	35	706	0.222
▼	60	18.1	26.6	208.2	0.041	0.023	0.0090	7.5	64	1354	0.167

TABLE III. *Pharmacokinetic parameters of thiopentone in eight elderly men. The data are calculated from the concentrations in venous blood after i.v. administration within 2 min of an induction dose (250–400 mg)*

Patient	Weight (kg)	V_1 (litre)	V_2 (litre)	V_3 (litre)	k_{12} (min^{-1})	k_{13} (min^{-1})	k_{10} (min^{-1})	$T_{\frac{1}{2}}^{\pi}$ (min)	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)	Cl (litre min^{-1})
□	79	12.3	29.1	125.3	0.050	0.021	0.017	7.3	94	984	0.209
■	97	14.1	29.9	152.0	0.079	0.032	0.016	4.5	52	798	0.225
○	75	6.0	15.0	118.1	0.085	0.047	0.046	3.5	41	612	0.277
●	86	4.5	29.5	69.6	0.214	0.053	0.036	2.1	65	590	0.165
△	73	16.9	47.7	282.8	0.098	0.017	0.015	4.4	94	1580	0.251
▲	68	3.3	17.6	60.1	0.230	0.068	0.054	1.8	45	470	0.178
▽	76	9.1	22.8	103.3	0.087	0.029	0.016	4.4	61	857	0.148
▼	83	11.8	35.0	86.9	0.259	0.025	0.028	1.8	51	440	0.332

The relationships between the rate constants k_{12} and the initial venous concentrations are shown in table IV. For the eight women the relationship was significant, but not for the eight men. It is seen that one male patient with a high k_{12} (0.259 min^{-1}) and a small serum concentration (18.3 μg ml^{-1}) greatly affected the value of the correlation coefficient. Among the women there was one with an average venous concentration but a prolonged k_{12} value (0.54 min^{-1}—more than 2SD from the average for the eight patients).

TABLE IV. *Statistical significance of the relationship between the rate constant* k_{12} *and the venous serum concentration at the moment of onset of sleep in elderly men and women*

	n	r	P
Women	8	0.92	<0.01
	7	0.81	<0.05
Men	8	0.38	n.s.
	7	0.78	<0.05

DISCUSSION

The methodology of the present study of elderly men and women was similar to that in our study of young men and women (Christensen, Andreasen and Jansen, 1980) and allows comparisons: elderly men and women (>60 yr) *v.* younger men and women (20–40 yr). For all 32 patients the elimination of thiopentone from serum could be described by a three-compartment open model (Christensen, Andreasen and Jansen, 1980).

Tables V-XI list differences of statistical significance between the four groups of patients.

Influence of sex

For younger patients the dose necessary for induction was significantly greater in the men; the same was true for the elderly patients (table V). If the doses were corrected for differences in body weight, men and women required the same dose. This was found for both age groups (table VI). This finding is in accord with our initial study in which the doses of thiopentone required to induce

TABLE V. *Average induction dose of thiopentone (mg ± SD) in young and elderly patients (eight patients in each of four groups)*

	20–40 yr	60–79 yr	
Women	319 ± 37	231 ± 25.8	$P<0.01$
Men	388 ± 52	312 ± 44.3	$P=0.02$
	$P<0.05$	$P<0.01$	

TABLE VI. *Average induction dose of thiopentone (mg per kg body weight ± SD) in young and elderly patients*

	20–40 yr	60–79 yr	
Women	5.43 ± 0.64	3.90 ± 0.68	$P<0.01$
Men	5.25 ± 1.05	3.97 ± 0.76	$P<0.05$
	n.s.	n.s.	

anaesthesia were compared in 540 patients studied over a 3-week period in our hospital (Christensen and Andreasen, 1978).

The concentration of thiopentone 20 s after the disappearance of the ciliary reflex was greater when the young men were compared with the young women, but the difference was not statistically significant. In the elderly the difference between the sexes was statistically significant (table VII). Thus, the distribution after administration of the same dose in mg per kg body weight differed between men and women. A relatively large apparent initial distribution volume in the women may reflect accumulation in certain more accessible tissues in the women than in the men. How this initial distribution pattern influences the effect is not clear. Calculations concerning the disposition of thiopentone to different tissues have been performed by Price and colleagues (1960) and by Bischoff and Dedrick (1968). A relatively rapid increase in the amount of the drug was found in the viscera (central nervous system, myocardium, kidneys, portal circulation). However, no attempt was made by these authors to distinguish between men and women.

TABLE VII. *The venous concentration (μg ml^{-1}) of thiopentone at the moment of onset of sleep (mean ± SD) in young and elderly patients*

	20–40 yr	60–79 yr	
Women	38.6 ± 24.1	19.2 ± 6.5	n.s.
Men	49.8 ± 19.7	34.3 ± 18.4	n.s.
	n.s.	$P<0.01$	

Average volumes of distribution are shown in tables VIII and IX. V_1, which is not shown, was about 30% greater in the elderly women than in the elderly men (n.s.) and 20% greater in the young women as compared with the young men. V_3 was almost three times as great in the young women as in the young men ($P<0.05$). In the elderly the difference was not significant. The values of V_2 do not show any significant differences. The elimination half-lives (table X) are shorter in the men, but only the differences between the two young groups are significant. For the plasma clearance none of the differences indicating a larger value for the men was significant (table XI).

TABLE VIII. V_2 *(litre) in young and elderly patients (mean with ranges)*

	20–40 yr	60–79 yr	
Women	12.4 (6.2–23.4)	20.9 (10.6–36.4)	$P<0.05$
Men	12.6 (6.0–22.9)	28.3 (15.0–47.7)	$P<0.05$
	n.s.	n.s.	

TABLE IX. V_3 *(litre) in young and elderly patients (mean with ranges)*

	20–40 yr	60–79 yr	
Women	92.8 (36.0–165.2)	161.3 (83.3–337.2)	$P<0.05$
Men	31.6 (19.4–44.3)	125.0 (60.1–282.8)	$P<0.01$
	$P<0.05$	n.s.	

TABLE X. $T_{\frac{1}{2}}^{\beta}$ *(min) in young and elderly patients (mean with ranges)*

	20–40 yr	60–79 yr	
Women	535 (273–1312)	990 (616–2223)	$P = 0.01$
Men	327 (206–473)	791 (440–1580)	$P < 0.01$
	$P<0.05$	n.s.	

TABLE XI. *Clearance (litre min^{-1}) in young and elderly patients (mean with ranges)*

	20–40 yr	60–79 yr	
Women	0.131 (0.047–0.209)	0.190 (0.137–0.269)	$P<0.05$
Men	0.164 (0.082–0.288)	0.220 (0.148–0.332)	n.s.
	n.s.	n.s.	

Influence of age

Significant decreases in induction dose in mg and in mg per kg body weight were seen with advancing age (tables V and VI); the decrease was about 25%. The findings are in accord with our previous study (Christensen and Andreasen, 1978) and with the results of Dundee (1954). Although the average venous serum concentration (table VII) seems considerably less in the elderly patients the differences are not statistically significant. The volumes of distribution became larger with increasing age. A 32–45% increase in V_1 was not significant, but V_2 and V_3 were significantly increased in the elderly patients (tables VIII and IX). V_3 in elderly men was increased almost fourfold. The average weight of the young men was 76 kg compared with 80 kg for the elderly. The two age groups of women had similar average body weight (young 59 kg and elderly 60 kg). It should be noted that Novak (1972) reported that body fat increased from 18 to 36% of the body weight when males of 18–25 yr of age were compared with males from 65–85 yr. In the same age groups he found an increase in women from 33 to 45%. An increased volume of distribution with advancing age has been found for diazepam (V^{ss}) (Klotz et al., 1975). No significant change with age was found for the distribution volumes of paracetamol, phenylbutazone, warfarin or sulphamethizole (Crooks, O'Malley and Stevenson, 1976). The terminal half-life of thiopentone (table X) was significantly increased with advancing age in both sex groups. Antipyrine (O'Malley et al., 1971; O'Malley, 1973; Vestal et al., 1975) and paracetamol (Briant et al., 1975; Triggs et al., 1975) have a prolonged $T_{\frac{1}{2}}$ in elderly patients. Diazepam (Klotz et al., 1975) and chlormethiazole (Nation et al., 1976) have significantly prolonged half-lives in elderly patients.

A higher clearance was found for thiopentone with advancing age in both women and men (table XI), but the difference was statistically significant only in the women. An increased clearance with advancing age was found for phenytoin in people older than 65 yr compared with people less than 45 yr by Hayes, Langman and Short (1975). A decreased binding of phenytoin was correlated with this increase in clearance. We (unpublished observations) have found a decrease in the binding of thiopentone to serum proteins in elderly patients.

In connection with our finding of prolonged $T_{\frac{1}{2}}$,

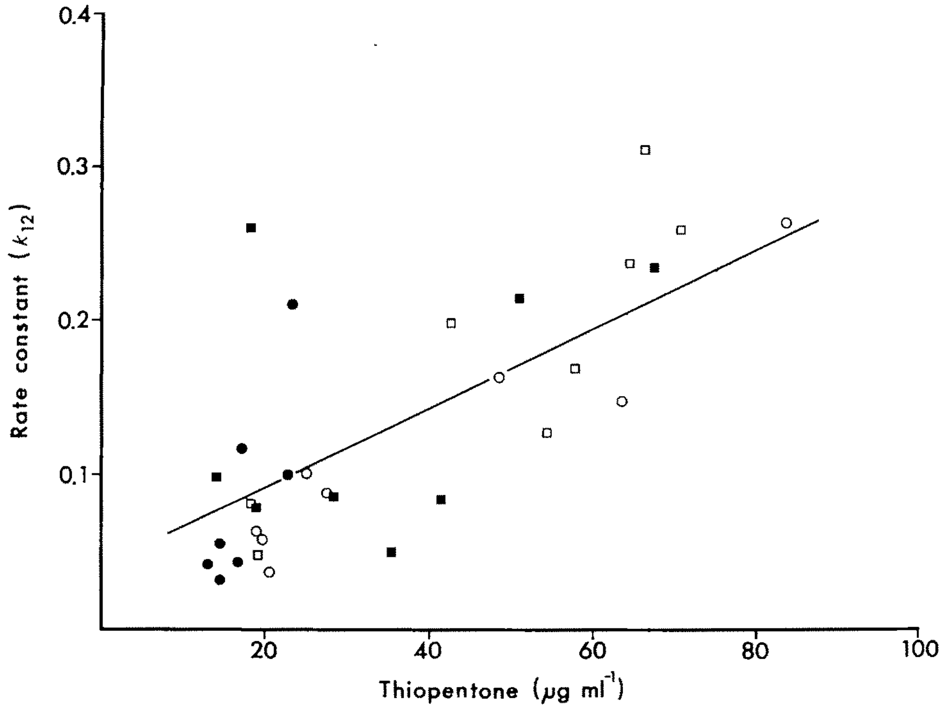

FIG. 2. The rate constant k_{12} (min^{-1}) as a function of the initial venous concentration of thiopentone in eight young women (○), eight young men (□), seven elderly women (●) and in eight elderly men (■). One elderly woman with an extreme k_{12} value (0.54 min^{-1}) is not shown. The correlation is significant for all 32 patients ($r = 0.49$, $P < 0.001$) as well as for the 31 patients shown ($r = 0.69$, $P < 0.001$).

larger volumes of distribution and a higher clearance for thiopentone with advancing age, it is interesting that the clearance of diazepam was found to be unchanged in elderly patients while V^{ss} was increased and the half-life was prolonged fourfold (Klotz et al., 1975).

Figure 2 shows the relationship between the initial venous concentration and k_{12} for 31 patients. The relationship confirms our previous finding that the rate constant (k_{12}) rather than the initial volume of distribution determines the dose necessary for induction.

k_{12} is probably determined by a combination of haemodynamic and diffusion parameters. Measurement of the initial arterial concentration may further contribute to the elucidation of the dose–concentration–effect relationship.

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INFLUENCE DE L'AGE ET DU SEXE SUR LA PHARMACOCINETIQUE DU THIOPENTONE

RESUME

On a administré du thiopentone à huit femmes et à huit hommes âgés de 60–79 ans. La disparition du thiopentone du sang veineux a été décrite par un modèle ouvert à trois compartiments. La seule différence significative entre les sexes a été une plus forte concentration veineuse initiale chez les hommes. La dose (mg kg^{-1}) utilisée pour l'induction a été de 70% de la valeur ($P<0,05$) signalée précédemment pour un groupe comparable de femmes et d'hommes plus jeunes (20–40 ans). Les volumes de répartition V_2 et V_3 ont été plus importants chez les personnes âgées ($P<0,05$). Les demi-vies terminales ont augmenté avec l'âge (de 75% à 100% en moyenne) ($P \leqslant 0,01$). La valeur d'elimination a été de 50% plus forte chez les femmes âgées que dans un groupe de jeunes femmes. Pour tous les groupes, une corrélation significative entre la concentration initiale de médicament et k_{12} soutient l'hypothèse que la constante du taux de redistribution k_{12} est le facteur prédominant du profil pharmacocinétique d'une dose de thiopentone suffisante pour obtenir un réflexe du cil.

EINFLUSS VON ALTER UND GESCHLECHT AUF DIE PHARMAKOKINETIK VON THIOPENTON

ZUSAMMENFASSUNG

Thiopenton wurde bei acht Frauen und acht Männern (60 bis 79 Jahre) verabreicht. Das Ausscheiden des Thiopentons aus dem Venenblut wurde mittels eines offenen Modells mit drei Abteilen beschrieben. Den einzigen bedeutenden Unterschied zwischen den Geschlechtern stellte eine höhere venöse Anfangskonzentration bei Männern dar. Die Induktionsdosis (mg kg^{-1}) entsprach 70% des Wertes ($P<0,05$), über den früher bei einer vergleichbaren Gruppe von jüngeren Männern und Frauen (20 bis 40 Jahre) berichtet wurde. Die Verteilungsvolumen V_2 und V_3 waren bei den älteren Patienten grösser ($P<0,05$). Die Terminalhalbwertzeiten wurden mit zunehmendem Alter gesteigert (von 75% auf 100% im Durchschnitt) ($P \leqslant 0,01$). Der Ausscheidungswert war um 50% grösser bei den älteren Frauen als bei einer Gruppe jüngerer Frauen. Eine bedeutende Korrelation zwischen der Anfangskonzentration und k_{12} bei allen Gruppen bekräftigte

die Hypothese, dass die Wiederverteilungsgeschwindigkeitskonstante k_{12} der überwiegende Faktor beim pharmakokinetischen Bild einer Thiopentondosis darstellt, die ausreicht, um den Augenwimperreflex zu dämpfen.

INFLUENCIA DE LA EDAD Y DEL SEXO EN LAS FARMACOCINETICAS DE LA TIOPENTONA

SUMARIO

Se administró tiopentona a ocho mujeres y a ocho hombres (de entre 60 y 79 años). La desaparición de la tiopentona de la sangre venosa se describe mediante un modelo abierto de tres compartimientos. La única diferencia significativa entre los sexos fue la de una mayor concentración venosa inicial en los hombres. La dosis ($mg\,kg^{-1}$) para la inducción fue 70% del valor ($P<0,05$) que se informó anteriormente y que correspondía a un grupo comparativo de mujeres y de hombres más jóvenes (de 20 a 40 años). Los volúmenes de distribución V_2 y V_3 fueron superiores en los individuos de mayor edad ($P<0,05$). Los periodos de vida media terminales aumentaron a medida que incrementaba la edad (un promedio de entre el 75% y el 100%) ($P<0,01$). El valor correspondiente a la eliminación fue un 50% superior en las mujeres de más edad que en lo relativo a un grupo de mujeres más jóvenes. En lo tocante a todos los grupos, una correlación significativa entre la concentración inicial de la droga y k_{12}, respaldó la hipótesis de que la constante del ritmo de redistribución, k_{12}, es el factor predominante en lo relativo a la farmacocinética de una dosis de tiopentona que sea suficiente como para anular el reflejo de la pestaña.

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USE OF DI-ISOPROPYL PHENOL AS MAIN AGENT FOR SHORT PROCEDURES

L. P. BRIGGS, R. S. J. CLARKE, J. W. DUNDEE, J. MOORE, M. BAHAR AND P. J. WRIGHT

SUMMARY

The use of di-isopropyl phenol (Diprivan) for induction of anaesthesia was assessed in doses ranging from 1 to 3 mg kg^{-1}. With less than 1.75 mg kg^{-1} not all patients were anaesthetized; 2.0 mg kg^{-1} appeared to be a satisfactory induction dose. Involuntary muscle movement, cough and hiccup at induction were rare with any dose studied. However, the frequency of hypotension and respiratory depression were related to the dose given. Pain on injection was uncommon when the drug was given into an antecubital vein, but occurred in 39% of patients when injected to the back of the hand or wrist. Recovery was rapid, and characterized by lack of emetic sequelae. Di-isopropyl phenol 1.5–2.0 mg kg^{-1} given rapidly during reactive hyperaemia can produce anaesthesia in one arm–brain circulation time. A reaction involving flush, hypotension, cough, laryngospasm and bronchospasm occurred in one patient receiving 2.5 mg kg^{-1} given over 20 s.

Di-isopropyl phenol (Diprivan; ICI 35 868) is an i.v. anaesthetic, sparingly soluble in water. Its clinical use was first described in 1977 by Kay and Rolly. Animal studies had shown that it was similar to methohexitone in potency and toxicity, with little evidence of cumulation. Kay and Rolly (1977a) found the optimum dose to be 1 mg kg^{-1}, which produced few side-effects and rapid recovery. However, with the original 2% formulation, in Cremophor EL and ethanol, pain occurred frequently along the vein to which the drug had been injected (Kay and Rolly, 1977b). This was found to be partly caused by the solvent and when a more dilute solution of 1% di-isopropyl phenol in Cremophor EL was used, the frequency and severity of pain on injection decreased to a level similar to that for methohexitone. Its animal pharmacology was described by Glen (1980) and preliminary findings in man by Rogers and his colleagues (1980). It has recently been compared with Althesin (Kay and Stephenson, 1980) and with methohexitone (Rutter et al., 1980).

The present study was designed to assess the optimum induction dose of di-isopropyl phenol and its local and general side-effects over a range of doses. In addition, speed and quality of recovery were assessed.

Rapidity of onset is desirable in an i.v. anaesthetic since it allows the dose to be titrated against effect during induction. A separate investigation was undertaken to determine the rate of onset of anaesthesia with di-isopropyl phenol.

METHODS

Healthy women undergoing minor gynaecological operations gave informed consent for the administration di-isopropyl phenol; any patient with a history of atopy or allergy (Watkins, Clarke and Fee, 1981) was excluded. As a result of previous reports of reactions with Cremophor-containing solutions (Huttel, Schou Oleson and Stoffersen, 1980) and the study by Glen and his colleagues (1979) on hypersensitivity reactions in the "mini-pig", any patient who had received a Cremophor-containing anaesthetic in the previous 6 months was also excluded.

Patients were not premedicated and were allocated at random to receive one of the selected doses (table I). The duration of anaesthesia and average total dose of the maintenance anaesthetic were broadly comparable. Di-isopropyl phenol was injected over 20 s to a convenient vein in the arm or hand. Each patient was asked "Is your arm quite comfortable?" and any complaint of pain was noted.

Anaesthesia was maintained with nitrous oxide 67% in oxygen and further 1-ml doses of the induction agent as required. If the patient failed to lose consciousness within 60 s, this was regarded as

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TABLE I. *Details of patients given a range of anaesthetic doses of di-isopropyl phenol*

Dose	1.0	1.5	1.75	2.0	2.5	3.0
Number	20	20	20	40	20	20
Average age (yr)	37	32	29	33	34	36
Average weight (kg)	58	59	59	58	60	60
Average total dose (mg kg^{-1})	3.1	3.2	3.3	3.5	3.3	3.4
Average duration (min)	9.0	9.1	8.0	9.9	8.5	6.4

absence of anaesthesia. The presence of excitatory effects (involuntary movements, tremor or hypertonus), respiratory upset (cough or hiccup) or respiratory depression (apnoea lasting for more than 15 s) was noted. Arterial pressure was measured by auscultation before induction and at 1-min intervals throughout anaesthesia.

At the end of surgery, the administration of nitrous oxide was discontinued and 2 min later each patient was assessed as awake, unconscious but with jaw tone, or unconscious without protective reflexes. At 1-min intervals the patient was asked to open her eyes and to give her date of birth, and the time was noted when she responded to these commands. The patient was questioned about nausea and vomiting approximately 1 and 6 h after the end of surgery.

The rate of onset of anaesthesia was investigated by injecting the drug to a large forearm vein as rapidly as possible during reactive hyperaemia following 3 min of circulatory occlusion (Clarke et al., 1968). In this way, the drug was carried rapidly centrally and the arm–brain circulation time was shortened and standardized. The onset time was studied in three groups of 20 patients with doses of 1.5, 1.75 and 2.0 mg kg^{-1} injected rapidly (1–3 s). The time from end of injection to cessation of counting was noted and, if the patient was not anaesthetized, the time was counted for averaging as 20 s.

RESULTS

Anaesthesia was successfully induced with the larger doses of ICI 35 868, but with the 1.0- and 1.5-mg kg^{-1} doses some patients failed to go to sleep (table II) and remained with the eyes open or talked or moved purposefully. There were few involuntary muscle movements, hiccup or other excitatory effects in any group and their occurrence was not dose-related. However, respiratory depression was dose-related and was marked in 75% of patients receiving 3.0 mg kg^{-1}. The maximum duration of apnoea was 2 min with 3.0 mg kg^{-1} and ventilation of the lungs was assisted easily in all patients. Hypotension was rare with doses up to 2 mg kg^{-1}, but was more frequent and severe as the dose was increased. The maximum decrease in systolic pressure was 50 mm Hg.

TABLE II. *Percentage of patients with various induction characteristics after a range of doses of di-isopropyl phenol given over 20 s*

	Dose (mg kg^{-1})					
	1.0	1.5	1.75	2.0	2.5	3.0
Anaesthesia induced	25	80	100	100	100	100
Excitatory effect	0	0	0	0	5	0
Respiratory upset	0	0	5	5	5	0
Marked respiratory depression	0	5	0	13	15	75
Decrease in systolic art. press. (mm Hg)						
20–40	0	5	0	5	30	50
40+	0	0	0	0	5	15

The frequency of pain on injection is shown in table III. Most of the patients complained of pain after 10–20 s and it extended along the vein of injection. The frequency of pain was 39% following injection to the back of hand or wrist and 3% following injection to one of the antecubital veins ($\chi^2 = 29.1$; $P < 0.0005$). There was no clear relation between size of vein and pain.

TABLE III. *Number of patients who complained of pain on injection after di-isopropyl phenol given to veins of various size at various sites (pooled doses)*

Site	Size	Patients	Number complaining of pain on injection
Antecubital	Large	73	3
	Medium	43	1
	Small	1	0
Wrist/hand	Medium	21	7
	Small	2	2
Total		140	13

With the doses of di-isopropyl phenol used in this study, recovery was rapid (table IV), nearly all the patients having regained the protective reflexes 2 min after discontinuing nitrous oxide. Ability to

TABLE IV. *Recovery after a range of doses of di-isopropyl phenol*

	Dose (mg kg^{-1})					
	1.0	1.5	1.75	2.0	2.5	3.0
2 min after anaesthesia:						
Awake (%)	50	40	15	25	35	30
Safe (%)	50	50	70	70	65	70
Time (min) to:						
Opening eyes on command	2.8	2.9	4.0	4.2	3.1	4.2
Giving date of birth	4.6	4.3	5.4	5.5	4.4	5.9
During first 6 h:						
Nausea (%)	0	10	10	5	0	0
Vomiting (%)	20	5	5	0	5	0

answer questions on the date of birth returned rapidly. The total dose of di-isopropyl phenol was similar in each group and recovery time was not related to the initial dose (table IV). Postoperative nausea and vomiting were rare but were more apparent with smaller doses.

When di-isopropyl phenol was given as rapidly as possible in adequate doses (1.75–2.0 mg kg^{-1}), it produced anaesthesia in one arm–brain circulation time (table V). The smaller dose (1.5 mg kg^{-1}) failed to induce anaesthesia in one patient and the average time for onset of anaesthesia was longer.

TABLE V. *Time (mean ± SEM) to cessation of counting in three groups of 20 patients given di-isopropyl phenol as rapidly as possible during reactive hyperaemia*

	Dose (mg kg^{-1})		
	1.5	1.75	2.0
Average age (yr)	38	33	40
Average weight (kg)	64	59	60
Onset of anaesth. (s)	13.5 ± 0.70	11.9 ± 0.58	10.5 ± 0.38

One of the patients who received di-isopropyl phenol 2.5 mg kg^{-1} over 20 s had an anaphylactoid reaction involving coughing which began 1 min following induction. Two minutes later the patient was given a further 20 mg on the assumption that anaesthesia was light, but further coughing with laryngospasm and bronchospasm followed. Cyanosis developed and persisted in spite of giving oxygen only to breathe. Three minutes after induction an urticarial rash was seen over the whole body. Arterial systolic pressure decreased from 110 mm Hg to 60 mm Hg at 3 min after the initial injection and hydrocortisone 500 mg, chlorpheniramine 10 mg and a rapid infusion of isotonic sodium lactate were given i.v.

The operative procedure was continued without nitrous oxide or further i.v. anaesthesia and recovery was uneventful, with opening of eyes 14 min after induction. Bronchospasm had disappeared completely within 20 min of anaesthesia; by this time some swelling of the eyelids which persisted for 12 h had developed. One week later the patient was anaesthetized for hysterectomy with thiopentone, pancuronium, fentanyl and nitrous oxide in oxygen. The anaesthetic was uneventful.

This patient, like all the others given di-isopropyl phenol in this study, had no history of atopy or allergy and no previous exposure to a Cremophor-containing anaesthetic. She appeared to be healthy. Plasma samples were taken serially and analysed for immunoglobulins and complement components (Watkins, Thornton and Clarke, 1979). The results, which suggest a true hypersensitivity, will be described elsewhere.

DISCUSSION

First studies with a new i.v. anaesthetic must be concerned with its potency and with determining a suitable anaesthetic dose. It was soon apparent that doses of less than 1.75 mg kg^{-1} of di-isopropyl phenol did not produce anaesthesia consistently. This is in contrast to the finding of Kay and Rolly (1977a) that 1.0 mg kg^{-1} was satisfactory. There is no obvious reason for this discrepancy other than a different criterion for minimum sleep dose. Certainly, for clinical practice, 2.0 mg kg^{-1} would be the most satisfactory induction dose and would appear to be comparable to thiopentone 4–5 mg kg^{-1}.

Di-isopropyl phenol can be classed as a rapidly-acting drug with an onset time comparable to that of thiopentone or methohexitone (Clarke et al., 1968) and quite different from ketamine (Bovill et al., 1971). This adds to the safety of the drug and its acceptability in clinical practice. Apart from drugs with slow onset of action such as ketamine or diazepam, onset of anaesthesia in clinical practice depends more on haemodynamic than on drug factors, as can be seen from the rapid injection studies.

Unlike some other induction agents evaluated in the past 20 years, such as methohexitone, etomidate or Althesin, di-isopropyl phenol does not evoke excitatory effects or hiccup in any of the doses studied. There were fewer side-effects than with thiopentone which has for long been regarded as ideal in this respect. However, there is a dose-related respiratory depression which is of no clinical importance at normal induction doses but becomes marked at 3.0 mg kg^{-1}. At this dose, 75% of patients exhibited apnoea lasting for more than 15 s and required ventilatory assistance. This is certainly more marked than with comparable doses of thiopentone, for only with thiopentone 14 mg kg^{-1} preceded by an opiate was such a degree of respiratory depression found (Clarke and Dundee, 1970). Further studies are needed to investigate this effect of di-isopropyl phenol. Arterial hypotension is not clinically important with a dose of 2.0 mg kg^{-1} but is marked with a dose of 3.0 mg kg^{-1}.

Pain on injection was a prominent feature of early reports of ICI 35868 (Kay and Rolly, 1977a, b). This was probably caused partly by the use of the 2% formulation of Cremophor EL with ethanol, but the adoption of the 1% formulation in Cremophor alone reduced injection pain to a level comparable to methohexitone (Kay and Rolly, 1977b). The present study has shown that pain on injection is still a marked disadvantage of the drug when given to peripheral arm veins. This relationship to site of injection rather than vein size may reflect that the pain does not develop for about 20 s and with more proximal injections the patient is usually asleep by this time. Certainly it was absent with the very rapid injection through a large cannula, and further (unpublished) observations suggest that it is more frequent with injections over 30–40 s. Alternatively it could be related to the rate of dilution which would be more rapid following injection to an antecubital than to a hand vein. The use of etomidate is also accompanied by pain and injections to the hand led to more pain than those into the forearm. Pain was also more frequent with small veins and slow injection speeds (Zacharias et al., 1978, 1979). There was no relationship in individual patients between pain on injection following etomidate and the development of phlebitis (Zacharias et al., 1979). It is therefore not surprising that studies of venous sequelae with di-isopropyl phenol have shown no relationship to previous pain and we found venous sequelae to be very rare.

Recovery following di-isopropyl phenol is satisfactory, although in our study few patients were awake 2 min after discontinuing nitrous oxide. The actual percentage varied between 25 and 50% whereas Dundee (1963), comparing all the barbiturates found a range between 30% for hexobarbitone and 80% for methohexitone. However, the majority of patients had regained protective reflexes at 2 min. There are no comparable figures yet for recovery of mental clarity, but the ability to give date of birth returned between 4 and 6 min after the end of anaesthesia which is very satisfactory clinically. The almost total absence of emetic sequelae (and often a desire for food) after anaesthesia with this drug is a major feature in its acceptability to the patient.

Di-isopropyl phenol is a drug with some advantages over existing induction agents, in particular the absence of excitatory effects and rapid recovery, free from sickness. However, the frequency of pain on injection is undesirable and the cardiovascular and respiratory despression when the normal induction dose is exceeded suggest a smaller safety margin than with Althesin.

The most important objection to di-isopropyl phenol is the use of Cremophor EL in the formulation. Evidence is accumulating to associate this solvent with hypersensitivity reactions (Watkins et al., 1976; Glen et al., 1979) and it is therefore highly desirable to find another solubilizing agent. The reaction encountered was not dangerous to the patient and resembles closely those seen with Althesin, but further reactions are to be anticipated. Since di-isopropyl phenol rather than the Cremophor EL is likely to cause pain on injection, this pain may remain as an undesirable feature, but it is brief in duration, whereas the hypersensitivity reactions are potentially life-threatening.

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USAGE DU DI-ISOPROPYLE PHENOL COMME AGENT ANESTHESIANT PRINCIPAL POUR LES INTERVENTIONS CHIRURGICALES DE COURTE DUREE

RESUME

On a fait usage de di-isopropyle phénol (Diprivan) pour l'induction de l'anesthésie en doses allant de 1 à 3 mg kg^{-1}. Avec moins de 1,75 mg kg^{-1}, il n'a pas été possible d'anesthésier tous les patients, mais 2 mg kg^{-1} semble avoir été une dose d'induction satisfaisante. Les mouvements musculaires involontaires, la toux et le hoquet, au moment de l'induction, ont été rares, quelle que soit la dose étudiée. Toutefois, la fréquence de l'hypotension et celle de la dépression respiratoire ont pu être reliées à la dose administrée. La douleur au moment de l'injection n'a pas été courante, lorsque cette injection a été faite dans une veine antécubitale, mais elle a été constatée dans 39% des cas, lorsque l'injection a été faite dans le dos de la main ou dans le poignet. La récupération a été rapide et a été caractérisée par un manque de séquelles émétiques. Le di-isopropyle phénol à raison de 1,5–2 mg kg^{-1} administré rapidement pendant une hyperémie réactive peut produire l'anesthésie dans un temps de circulation bras–cerveau. Il s'est produit une réaction entraînant bouffées de chaleur, hypotension, toux, laryngospasme et bronchospasme chez un malade auquel on avait administré 2,5 mg kg^{-1} en 20 secondes.

DIE VERWENDUNG VON DI-ISOPROPYLPHENOL ALS HAUPTNARKOSEMITTEL BEI KURZEN OPERATIONEN

ZUSAMMENFASSUNG

Di-Isopropylphenol (Diprivan) wurde in Dosen zwischen 1–3 mg kg^{-1} zur Induktion der Anästhesie verwendet. Bei weniger als 1,75 mg kg^{-1} wurden nicht alle Patienten betäubt; 2,0 mg kg^{-1} scheint eine hinreichende Induktionsdosis darzustellen. Unwillkürliche Muskelbewegungen, Husten und Schluckauf bei der Induktion kamen selten vor bei den Dosen, die hier studiert wurden. Die Häufigkeit von Hypertropie und Atmungsdepression stand jedoch in Beziehung mit den verabreichten Dosen. Als die Droge in eine vorulnäre Vene injiziert wurde, gab es selten Schmerzen, aber 39% der Patienten empfanden Schmerzen, als die Droge in den Handrücken oder in das Handegelenk injiziert wurde. Sie erholten sich aber schnell und ohne Brechreiz. Wenn Di-Isopropylphenol 1,5–2,0 mg kg^{-1} schnell während reaktiver Hyperämie verabreicht wird, kann die Anästhesie mit Zirkulationsgeschwindigkeit eintreten. Eine Reaktion, die aus Röte, Hypertropie, Husten, Laryngospasmus und Brochospasmus bestand, stellte sich bei einem Patienten ein, der 2,5 mg kg^{-1} innerhalb 20 Sekunden bekam.

USO DEL DI-ISOPROPILA FENOLICO CUAL AGENTE PRINCIPAL PARA PROCEDIMIENTOS DE CORTA DURACION

SUMARIO

El uso de di-isopropilo fenólico (Diprivan) para inducir anestesia se administró en dosis que oscilaron entre 1 y 3 mg kg^{-1}. No todos los pacientes quedaron anestesiados cuando se les administro una cantidad inferior a 1,75 mg kg^{-1}; la dosis de inducción que pareció ser satisfactoria fue de 2,0 mg kg^{-1}. Con todas las dosis que se estudiaron, el movimiento muscular involuntario, la tos y el hipo, durante la inducción, fueron algo poco frecuente. No obstante, la frecuencia de la hipotensión y de la depresión respiratoria vinieron relacionadas con la dosis administrada. El dolor como consecuencia de la inyección fue poco común cuando la droga se administró en una vena antecubital, pero se presentó en el 39% de los pacientes cuando la inyección se efectuó en la parte

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TWO-STAGE INFUSION OF CHLORMETHIAZOLE FOR BASAL SEDATION

L. T. Seow, J. G. Roberts, L. E. Mather and M. J. Cousins

SUMMARY

The effectiveness of chlormethiazole in providing basal sedation was studied using a two-stage infusion regimen consisting of an initial loading dose of 60 mg min^{-1} for 25 min (in the lateral position) followed by a maintenance constant-rate infusion of 10 mg min^{-1} for 60 min (in the supine position). The regimen was evaluated in five healthy young volunteers who were all moderately sedated throughout most of the infusion, lapsing into sleep when left undisturbed, yet awakened easily to obey commands. Varying periods of amnesia, corresponding with a mean chlormethiazole ethanedisulphonate blood concentration of 10.3 mg litre^{-1} (SD 3.8) were obtained. Light sedation occurred during the first 10 min and the last 20 min of the total infusion period, corresponding to chlormethiazole blood concentrations of 7.9 mg litre^{-1} (SD 1.9) and 7.4 mg litre^{-1}(SD 2.3) respectively. Adverse side-effects were transient nasal irritation, flushing and a coryza-like syndrome. Other side-effects of tachycardia and hypertension may be beneficial in counteracting cardiovascular depression associated with central neural blockade. A high total body clearance of chlormethiazole (mean 1.39 litre min^{-1}, SD 0.58) was found and would contribute to the brief duration of action after termination of the infusion.

An increasing number of radiological, endoscopic and major surgical procedures are performed under topical, local or regional analgesia and many of the patients require some form of sedation or narcosis. Narcosis induced by nitrous oxide has been used, but was limited by problems of insufficient depth of unconsciousness and unpleasant dreams. The use of a volatile agent such as halothane to produce narcosis may produce decreases in cardiac output, bradycardia or loss of airway support. Thus the development of an i.v. sedative technique, which produces minimal cardiorespiratory depression, maintains airway reflexes and provides amnesia would be a distinct advantage.

Precise control of the level of sedation during regional analgesia has posed a challange to the anaesthetist. A variety of central nervous system (c.n.s.) depressant agents, administered in different doses and regimens, together with various psychological approaches to patients, has been used. Most of these suffer from complex dose regimens or prolonged drowsiness following surgery because of the use of long-acting drugs. Recent studies have suggested that chlormethiazole may be valuable in this context (Mather and Cousins, 1980; Seow, Mather and Roberts, 1981).

This study was designed to assess the efficacy of a two-stage infusion of chlormethiazole in maintaining a state of basal sedation similar to that required during operations performed under regional anaesthesia. This was tested in young healthy volunteer subjects, in the absence of surgical stress and concomitant drugs. During this study pharmacokinetic and pharmacodynamic characteristics of chlormethiazole were determined in relation to those postural changes often encountered during the performance of extradural or spinal blockade. Volunteer studies of this kind are a prerequisite to the design of safe clinical trials in patients and any differences occurring between the volunteers and patients help to elucidate the physiology of patients presenting for surgery.

SUBJECTS AND METHODS

Five healthy adult volunteers, aged 18–21 yr, and weighing 49–80 kg were studied (table I). Informed consent was obtained after a detailed explanation of the plan. Criteria for selection of the subjects, preparation for the study and the monitoring of the subjects, were as described previously (Mather et al., 1981; Seow, Mather and Roberts, 1981). After a rest period of 1 h following insertion of i.v. lines, the clearance of indocyanine

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TABLE I. *Physical characteristics of volunteer subjects*

	Subject number						
	1	2	3	4	5	Mean	SD
Age (yr)	21	20	18	19	19	19	1
Sex	M	M	F	M	F	—	—
Weight (kg)	64	69	49	80	50	62	13
Height (cm)	176	180	161	192	151	172	15

green (Austin, Stapleton and Mather, 1981) was determined in all subjects in the supine position and, in four subjects, in the left lateral position 30 min later, to evaluate the postural effects which may alter liver blood flow and the blood concentrations of chlormethiazole.

Chlormethiazole ethanedisulphonate 0.8% (Heminevrin, CTZ) was administered by a two-stage infusion, designed to achieve a moderately sedated clinical state:

(a) A *loading infusion* of 60 mg min^{-1} CTZ (7.5 ml min^{-1}) was administered at a constant rate for 25 min with the subject in the left lateral position, followed immediately by:

(b) A *maintenance infusion* of 10 mg min^{-1} CTZ (1.25 ml min^{-1}) at a constant rate for 60 min, with the subject supine.

The CTZ solution was infused with a Braun "Infusomat" pump into a left antecubital vein. Throughout the infusion, arterial pressure, heart rate and respiratory rate were monitored at 5-min intervals whilst finger plethysmography, e.c.g., skin temperature and state of consciousness were monitored continuously. Higher mental faculties were assessed every 15 min by a psychometric test called Paced Auditory Serial Addition Tasks (PASAT) (Gronwall and Sampson, 1974; Mather et al., 1981).

Blood samples (1.0 ml) for CTZ analyses were taken from the contralateral axillary vein at the following times: before commencing infusion, every 5 min for 45 min (during the 25 min of loading infusion and for first 20 min of maintenance infusion), every 10 min until the end of the infusion, every 5 min for 20 min after cessation of infusion, every 10 min for the next 20 min and then at 20-min intervals for the next 4 h. Axillary vein blood rather than central venous blood was obtained to avoid sampling blood enriched with CTZ being infused in the contralateral antecubital vein. A non-linear least squares routine on a digital computer was used to derive empirical biexponential equations corrected for double infusions which described the relationship between blood concentrations and time (Mather, Ringrose and Austin, 1979). From the coefficients and exponents of these equations, the constants of a two-compartment open model were derived (Austin, Stapleton and Mather, 1981).

CTZ analyses were performed using a solvent extraction (Mather and Tucker, 1974) and gas chromatographic analysis technique similar to that recently reported by Tsuei, Thomas and Nation (1980) except that an OV 225 column was used. Accuracy and sensitivity were the same as those reported by Tsuei, Thomas and Nation and the OV 225 column also resolved CTZ and its internal standard bromethiazole (BTZ), from two of its prime metabolites, the ketone (5-acetyl-4 methylthiazole; AMT) and the secondary alcohol (5-(-1-hydroxyethyl)-4-methylthiazole;HEMT), both formed by oxidation of the chlorethyl side chain (Moore, Robertson et al., 1975; Nation et al., 1977). An additional metabolite was noted in gas chromatograms but was not measured as no authentic reference substance was available. This metabolite was subjected to structural analysis using combined gas chromatography–mass spectrometry. For this analysis, the same gas chromatographic conditions were used to separate the compounds. The instrument used was a Hewlett–Parkard Model 5995 gas chromatograph–mass spectrometer operating with electron impact ionization at 70 eV.

RESULTS

The physical characteristics of the subjects are shown in table I. Each subject received CTZ 60 mg min^{-1} for 25 min in the left lateral position (one subject (No. 3) received this regimen for 20 min only as she was deeply sedated at that time). The subsequent constant-rate infusion of 10 mg min^{-1} was administered to all subjects in the supine position for 60 min.

A representative curve of blood CTZ concentrations (expressed as the salt in mg $litre^{-1}$) plotted against time, during and after infusion, is shown in figure 1. CTZ blood concentrations increased rapidly with the loading infusion. A very light level of sedation, associated with yawning, occurred in all subjects, 7–10 min after commencing the infusion; the mean CTZ blood concentration was 7.9 mg $litre^{-1}$ (SD 1.9). The maximum CTZ blood concentrations were achieved in all

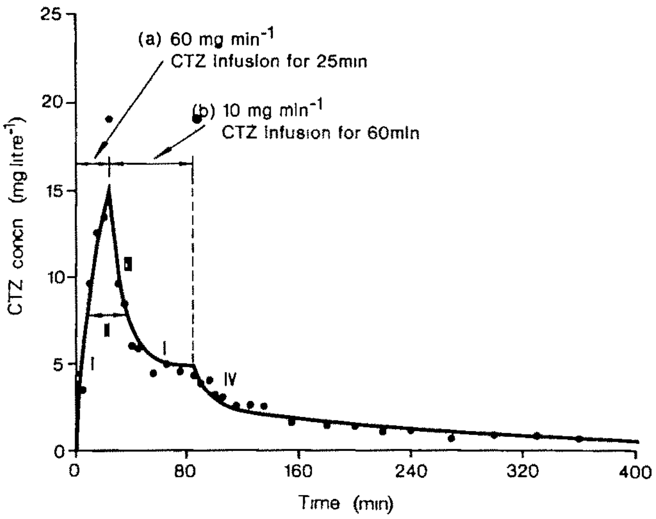

FIG. 1. Blood concentrations of chlormethiazole (mg litre^{-1} salt) following a two-stage infusion regimen consisting of (a) 60 mg min^{-1} (0.8% CTZ 7.5 ml min^{-1}) for 25 min; (b) 10 mg min^{-1} (1.25 ml min^{-1}) for 60 min in one subject (No. 2). The continuous line depicts a computer-fitted curve describing two-compartment open model kinetics. I = Light sedation; II = moderate sedation with amnesia; III, IV = rapid decrease in blood CTZ concentrations reflecting rapid redistribution.

subjects at the end of the loading infusion and ranged from 11.3 mg litre^{-1} (associated with a clinical state of moderate sedation) to 25.1 mg litre^{-1} (deeply sedated), with a mean value of 18.5 mg litre^{-1} (SD 5.0) (table II). However, with the commencement of the maintenance infusion the initially high CTZ blood concentrations were not sustained, but decreased rapidly to reach a plateau during the last 20 min of infusion. Thoughout most of the loading infusion (except for subject No. 3 who was deeply sedated for 2 min) all other subjects were moderately sedated. They lapsed into a sleep-like state when left undisturbed, but were easily aroused to obey commands; while awake, all would agree to do the psychometric test, PASAT, but would lapse into sleep almost immediately after starting the test. This state was associated with a varying period of amnesia in all subjects (mean 44 min, SD 36) occurring 15 min after commencement of the loading infusion, and, in two subjects, continuing for 10–20 min after cessation of the whole infusion. Amnesia occurred at a mean CTZ blood concentration greater than 10.3 mg litre^{-1} (SD 3.8) (table II).

The mean CTZ blood concentration over the last 20 min of infusion and at the cessation of infusion was 7.4 mg litre^{-1} (SD 2.3), corresponding to a very light degree of sedation only. Recovery was rapid and, by 1 h after infusion, all

TABLE II. *(1) = Maximum chlormethiazole (CTZ) blood concentration measured. Values in parentheses indicate maximum concentration predicted from two-compartment model data; (2) = concentration at amnesia; (3) = light sedation occurred; (4) = concentration at end of infusion; (5) = 1 h after infusion; (6) = 4 h after infusion. *Subject 3 was deeply sedated*

	Subject number						
	1	2	3*	4	5	Mean	SD
(1) C_{max} (mg litre^{-1})	20.3 (19.4)	18.6 (15.3)	25.1 (22.3)	17.1 (13.2)	11.3 (10.6)	18.5 (16.2)	5.0 (4.7)
(2) $C_{amnesia}$ (mg litre^{-1})	16.2	10.6	10.5	6.9	7.2	10.3	3.8
(3) C_{light} (mg litre^{-1})	9.0	9.2	9.6	6.3	5.5	7.9	1.9
(4) C_{end} (mg litre^{-1})	10.0	6.0	9.7	6.9	4.7	7.4	2.3
(5) $C_{1\text{-}h}$ (mg litre^{-1})	5.2	2.0	2.5	2.4	1.8	2.8	1.4
(6) $C_{4\text{-}h}$ (mg litre^{-1})	1.5	0.92	1.3	0.63	0.7	1.0	0.4

subjects were complaining of hunger and were engaged in rational conversation or reading. The mean CTZ blood concentration 1 h after infusion was 2.8 mg litre^{-1} (SD 1.4).

Derived pharmacokinetic parameters are shown in table III. Total body clearance of chlormethiazole was rapid (mean 1.39 litre min^{-1}, SD 0.58), about one to one-and-a-half times that of indocyanine green (ICG). Renal clearance of chlormethiazole was negligible (mean 1.9 ml min^{-1}, SD 1.1), being less than 0.14% of the total body clearance. The rapid decline in blood concentrations of CTZ immediately following the change from the loading to the maintenance infusion regimen, as well as immediately following cessation of maintenance infusion (fig. 1) reflected a rapid . redistribution phase ($T_{\frac{1}{2}}^{\alpha}$ = 14 min, table III). This is consistent with the observation that V^{ss} was several times V_1 (table III). The mean elimination half-life was 214 min, with considerable variation between subjects (SD 155 min). In three of four subjects in whom ICG clearance was estimated in both the supine and lateral positions, a lower clearance was found in the lateral position. However, there was no statistically significant difference in ICG pharmacokinetics as a function of position. ICG clearance is not synonymous with liver blood flow, which is obtained from the quotient of ICG clearance and ICG extraction ratio with steady-state conditions. However, ICG clearance is a useful reference point for the individual clearance of a flow-limited drug.

All subjects reported nasal irritation, nasal congestion, lacrimation and facial flush 2–5 min after commencement of the infusion. Tachycardia occurred invariably, with a mean increase in heart rate of 34 beat min^{-1} (SD 10), a 50% increase from the pre-infusion value, 5–10 min after commencing the infusion (fig. 2). This coincided with a moderately sedated state; the heart rate returned to pre-infusion values in all subjects as the degree of sedation lightened (and CTZ blood concentrations

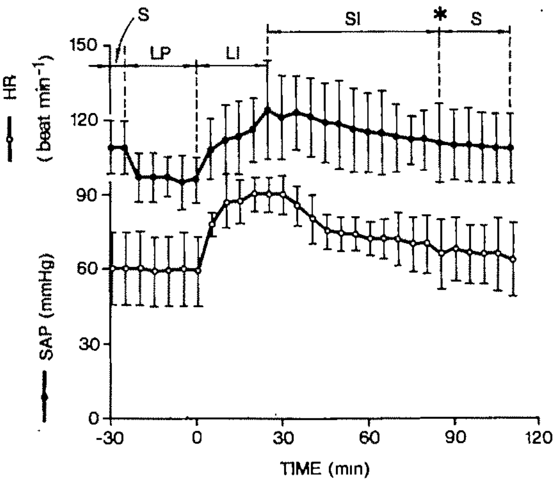

FIG. 2. Mean values (with SD) of arterial pressure (●——●) and heart rate (○——○) monitoring before, during and after chlormethiazole infusion. S = Supine position: no infusion; LP = lateral position: no infusion; LI = lateral position: CTZ infusion of 60 mg min^{-1} for 25 min; SI = supine position: CTZ infusion of 10 mg min^{-1} for 60 min; *end of infusion.

TABLE III. *Infusion characteristics and derived pharmacokinetic parameters. (1) = Total body clearance (blood); (2) = renal clearance; (3) = initial dilution volume; (4) = volume of distribution at steady-state equilibrium; (5) = fast or "redistribution" half-life; (6) = slow or "elimination" half-life; (7) = ICG total body clearance (blood), lateral position; (8) = ICG total body clearance (blood), supine position*

	Subject number						
	1	2	3	4	5	Mean	SD
Infusion regime (mg min^{-1})	60→10	60→10	60→10	60→10	60→10		
Infusion time (min)	25→60	25→60	20→60	25→60	25→60		
(1) Cl_B (litre min^{-1})	0.98	1.68	0.69	1.44	2.17	1.39	0.58
(2) Cl_R (ml min^{-1})	1.8	1.6	0.6	1.7	3.7	1.9	1.1
(3) V_1 (litre)	37	39	38	84	88	57	26
(4) V^{ss} (litre)	114	235	273	239	218	216	60
(5) $T_{\frac{1}{2}}^{\alpha}$ (min)	7	7	17	24	13	14	7
(6) $T_{\frac{1}{2}}^{\beta}$ (min)	101	156	476	230	108	214	155
(7) ICG_B^{lat} (litre min^{-1})	—	0.86	0.50	0.75	0.94	0.76	0.19
(8) ICG_B^{sup} (litre min^{-1})	0.97	1.11	0.54	0.70	1.03	0.87	0.24

TABLE IV. *Metabolite concentrations in blood (read in conjunction with CTZ data in table II). *Approximate concentration only as no authentic reference compound available. Calculated as CTZ. Known to be unstable, hence these values represent minimal values*

	Subject number				
Metabolite concentration	1	2	3	4	5
AMT					
End of infusion (mg litre^{-1})	0.2	0.3	0.4	0.2	0.5
4 h after infusion (mg litre^{-1})	0.3	0.3	0.4	0.2	0.4
Maximum (mg litre^{-1})	0.3	0.4	0.5	0.3	0.5
Time of maximum (min)	240	135	50	300	100
Aldehyde metabolite 1*					
End of infusion (mg litre^{-1})	1.8	1.5	4.0	2.4	3.5
4 h after infusion (mg litre^{-1})	2.5	1.0	2.1	1.2	1.0
Maximum (mg litre^{-1})	3.2	2.1	7.1	3.3	3.9
Time of maximum (min)	145	105	50	100	90

decreased). Before infusion, a change from the supine to the lateral position resulted in a 12% decrease in systolic arterial pressure (SAP) in all subjects (mean 13 mmHg, SD 4). SAP increased during CTZ infusion, with a mean maximum increase of 27% occurring at the end of the initial loading infusion. As sedation lightened, SAP also returned to the pre-infusion values in all subjects.

Two metabolites of CTZ, the secondary alcohol and the ketone, were identified from gas chromatograms of the blood and urine extracts. The retention times for bromethiazole (internal standard), chlormethiazole, secondary alcohol and ketone metabolites were respectively 4.2 min, 2.7 min, 3.7 min and 2.1 min. The blood concentrations of the secondary alcohol metabolite were small (less than 0.1 mg litre^{-1}). The ketone metabolite concentration in blood was small compared with that of chlormethiazole (table IV). Another metabolite with a retention time of 3.4 min was present in all blood samples after the commencement of the infusion. Its concentration increased with time up to about 2 h and exceeded that of chlormethiazole (table IV). The retention time corresponded to that of aldehyde also formed by chlormethiazole side-chain oxidation and mass spectral analysis has confirmed this. The aldehyde would be expected to be unstable and it is likely that it was found in blood in the present analysis because of careful cold storage of blood specimens and rapid processing before chromatography.

DISCUSSION

Laborit and colleagues (1957) demonstrated the rapid hypnotic action of CTZ following i.v. injection. The need for large volumes of CTZ to induce anaesthesia and the relatively slow onset of action militated against its usefulness as an induction agent for general anaesthesia. However, its value as a basal sedative and hypnotic in patients undergoing surgery under regional analgesia appears to have been overlooked. Different techniques of CTZ infusion have been suggested to provide supplementation to extradural analgesia. Wilson (1972) suggested induction of anaesthesia using a barbiturate followed by i.v. infusion of 0.8% CTZ to maintain sleep. Schweitzer (1978) used a high loading dose of 20 ml min^{-1} for 3 min to produce sleep, maintaining sleep with an hourly graduated infusion regimen which decreased from 210 to 50 ml h^{-1}. In both these studies, extradural blockade was instituted after the onset of sleep. Mather and Cousins (1980) commenced a two-stage infusion based on the administration of 190 ml (1520 mg) over 30 min to induce sleep only after the extradural block was established, followed by a maintenance infusion of 75 ml (600 mg) per hour. Based on the results of these studies and a wider clinical experience, we recommend induction of sedation with CTZ, while the extradural block is being performed to shorten the total time required. This would greatly increase the comfort of the patient during extradural block and probably produce amnesia for the procedure. However, modification of the infusion rates would be required in the aged, others in whom CTZ clearance is diminished (Nation et al., 1976; Pentikainen, Neuvonen and Jostell, 1980), if there was recent administration of sedative or psychotropic drugs and if the degree of sedation was insufficient. A person other than the one performing the extradural block should monitor continuously the state of consciousness, airway and vital signs of the patient.

Amnesia from chlormethiazole has been reported previously (Wilson, 1972; Schweitzer, 1978; Mather and Cousins, 1980) and was found in all of our subjects. Whilst Schweitzer reported complete amnesia extending for several hours following surgery, the period of amnesia in our subjects lasted for the period of infusion, extending to 10–20 min after cessation of infusion in two subjects. However, Schweitzer's patients were premedicated with papaveretum and hyoscine, and the contribution of hyoscine to the amnesia is difficult to estimate. Premedication certainly does contribute to the quality of sedation during the operation (Gjessing and Tomlin, 1977), while premedication with hyoscine has been shown to contribute to amnesia after operation (Lambrechts and Parkhouse, 1961). Our study in volunteer subjects, without the influence of any other drugs, would suggest that postoperative anterograde amnesia does not result from chlormethiazole infusions if the CTZ blood concentrations decreases to less than about 10 mg litre^{-1}.

The CTZ blood concentration producing this ideal sedated state is similar to that obtained in a previous study by Mather and Cousins (1980), who found that the sleep state occurred at a CTZ blood concentration of 6.7 mg litre^{-1} base (10.5 mg litre^{-1} salt). Scott and colleagues (1980) found that unconsciousness was associated with plasma concentrations (base) in the range 3–5 μg ml^{-1} (5.4–7.8 mg litre^{-1} salt). This smaller value may have resulted from the poorer physical condition of their patients, who were all undergoing intensive care, and the presence of other sedative and opiate drugs.

Recovery from the effects of chlormethiazole is rapid after short infusions of up to 3 h (Wilson, 1972; Schweitzer, 1978; Mather and Cousins, 1980). This is probably related to the high clearance of the drug (Moore, Triggs et al., 1975; Nation et al., 1976) being one to about one-and-a-half times that of indocyanine green (Seow, Mather and Roberts, 1981). In addition, the high clearance suggests that any systemic disturbances which alter liver blood flow, rather than changes in hepatic metabolism, could increase blood concentrations and exaggerate the clinical effects. High clearance is a desirable property of an i.v. sedative agent as it produces easy control of the depth of sedation and allows rapid awakening on termination of the infusion. Benzodiazepines (Scott, 1975; Gjessing and Tomlin, 1977) and Althesin (Dixon et al., 1976) have been advocated for this purpose. Unfortunately, the benzodiazepines are eliminated slowly: the total body clearance of diazepam is 0.02–0.03 litre min^{-1} with a half-life of approximately 30 h in normal man (Klotz et al., 1975). Althesin has ideal pharmacokinetic characteristics (high plama clearance of 1.43 litre min^{-1}) and short elimination half-life (34 min) (Simpson, 1978); but the frequency of hypersensitivity, ranging from 1 : 900 (Watt, 1975) to 1 : 1900 (Evans and Keogh, 1977) must limit its use. Chlormethiazole is suggested as a suitable alternative for short-term sedation for up to a few hours. Prolonged infusion for up to 48 h has been shown to be associated with delayed recovery during intensive care (Scott et al., 1980), but this remains to be confirmed in healthy patients. This suggests cumulative effects from prolonged infusion, and would necessitate the gradual reduction of the rate of infusion to maintain the same degree of sedation. Three metabolites were measured in blood, and these were found to increase in concentration significantly over the period of the study. Whether these metabolites are active in man and contribute to the sedative state during prolonged infusion, warrants further investigation. Reasons for the differences in blood concentrations of HEMT found in the present study and by others (Nation et al., 1977; Tsuei, Thomas and Nation, 1980) are not apparent.

Tachycardia is a recognized feature of chlormethiazole infusion. Wilson, Stephen and Scott (1969) reported an average increase of 48.7% over resting heart rate in volunteers, which is comparable to the 50% in our series, although the heart rate decreased to its pre-infusion value as sedation lightened. The clinical importance of this depends upon the baseline heart rate, but the effect might be useful in the treatment of bradycardia secondary to extradural or spinal analgesia. Galizia, Metreweli and Prout (1975) used chlormethiazole to sedate patients who developed bradycardia as a result of a recent myocardial infarct. Wilson, Stephen and Scott (1969) demonstrated the remarkable stability of mean arterial pressure following chlormethiazole infusion in volunteers. This is contrary to our findings of an increase of 27% in systolic pressure, which was evident once the patients were moderately sedated. Although Schweitzer (1978) noted stability of arterial pressure following induction of sleep, any effect of chlormethiazole on arterial pressure in that study would be masked by the subsequent institution of extradural blockade.

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PERFUSION DE CHLOROMETHIAZOLE EN DEUX TEMPS POUR OBTENIR UNE SEDATION DE BASE

RESUME

Nous avons fait une étude pour déterminer l'efficacité du chlorométhiazole lorsqu'on souhaitait obtenir une sédation de base, en utilisant une régime de perfusion en deux temps comprenant une dose de charge initiale de $60\,\mathrm{mg\,min^{-1}}$ pendant 25 min (dans la position latérale), suivie d'une perfusion d'entretien à débit constant de $10\,\mathrm{mg\,min^{-1}}$ pendant 60 mn (dans la position couchée). Ce régime a été évalué sur cinq jeunes volontaires en bonne santé, lesquels étaient modérément assoupis pendant la plus grande partie de la perfusion, s'endormant lorsqu'on ne les dérangeait pas, mais pouvant toutefois être éveillés facilement pour obéir aux commandements. Nous avons obtenu des périodes d'amnésie variables, correspondant

à une concentration moyenne de 10,3 mg litre^{-1} (écart type 3,8) de chloromethiazole éthanedisulfonate dans le sang. On a constaté une légère sédation pendant les premières 10 min et les dernières 20 min de la durée totale de la perfusion, correspondant respectivement à des concentrations de 7,9 mg litre^{-1} (écart type: 1,9) et de 7,4 mg litre^{-1} (écart type 2,3) de chlorométhiazole dans le sang. Parmi les effets secondaires indésirables, il y a eu une irritation nasale transitoire, des rougeurs et un syndrome ressemblant à un rhume de cerveau. Les autres effets secondaires: tachycardie et hypertension, peuvent être bénéfiques pour neutraliser la dépression cardiovasculaire associée à un blocage nerveux central. On a trouvé un fort coefficient d'épuration du chlorométhiazole du corps (moyenne 1,39 litre min^{-1}, écart type 0,58) et cela contribue à la bréve durée d'action après la cessation de la perfusion.

ZWEISTUFIGE INFUSION VON CHLORMETHIAZOL ALS GRUNDBERUHIGUNGSMITTEL

ZUSAMMENFASSUNG

Die Wirkung von Chlormethiazol als Grundberuhigungsmittel wurde mittels einer zweistufigen Infusionstechnik studiert, die aus einer Belastungsdosis von 60 mg min^{-1} über 25 Min in der Seitenlage mit anschliessender kontinuierlicher Fortsetzungsinfusion von 10 mg min^{-1} über 60 Min in der Rückenlage bestand. Diese Technik wurde bei fünf gesunden jungen Freiwilligen ausgewertet, die alle die meiste Zeit während der Infusion leicht beruhigt waren und jedes Mal einschliefen, wenn sie in Ruhe gelassen wurden, aber doch leicht geweckt werden konnten, um Befehle auszuführen. Es wurden verschieden lange Perioden von Amnesie erreicht, die einer mittleren Chlormethiazol-Ethandisulphonat-Blutkonzentration von 10,3 mg litre^{-1} entsprachen (SD 3,8). Leichte Beruhigung erfolgte während der ersten 10 Min und der letzten 20 Min der Gesamtinfusionszeit, was Chlormethiazol-Blutkonzentrationen von 7,9 mg litre^{-1} (SD 1,9) bzw. 7,4 mg litre^{-1} (SD 2,3) entsprach. Als nachteilige Seiteneffekte wurden vorübergehender Juchreiz in der Nase, Röte und ein Coryzaähnliches Syndrom festgestellt. Andere Seiteneffekte von Tachykardia und Hypertonie könnten vielleicht bei der Bekämpfung der kardiovaskulären Depression von Nutzen sein, die mit der Zentralnervenblockade verbunden ist. Es wurde eine hohe Gesamtausscheidung von Chlormethiazol (Durchschnitt, 1,39 litre min^{-1}, SD 0,58) festgestellt, was zur kurzen Wirkungsdauer nach Beendigung der Infusion beitragen würde.

INFUSION DE CLOROMETIAZOLA EN DOS FASES PARA LA SEDACION BASAL

SUMARIO

Se estudió la efectividad de la clorometiazola para proveer sedación basal, usando un régimen de infusión de dos fases, consistente de una dosis de carga inicial igual a 60 mg min^{-1} por espacio de 25 min (en la posición lateral), seguida de una infusión de mantenimiento de régimen constante igual a 10 mg min^{-1} por espacio de 60 min (en la posición de supino). El régimen se evaluó en cinco jóvenes voluntarios y sanos quienes sufrieron sedación moderamente durante la mayor parte de la infusión, quedándose dormidos al quedarse solos, y pudiendo despertarse con facilidad para obedecer las órdenes que se les dieran. Se obtuvieron períodos variables de amnesia que correspondieron con una concentración media de 10,3 mg litro^{-1} de etanodisulfonato de clorometiazola en la sangre (Desviación Típica de 3,8). Durante los 10 min iniciales y durante los últimos 20 min del período total de la infusión se presentó una ligera sedación, correspondiendo a concentraciones de 7,9 mg litro^{-1} (Desviación Típica de 1,9) y de 7,4 mg litro^{-1} (Desviación Típica de 2,3) de clorometiazola en la sangre, respectivamente. Los efectos secundarios negarivos fueron la irritación momentánea nasal, el sonrojo de las mejillas y el síndrome del tipo coriza. Otros efectos secundarios de la taquicardia y de la hipertensión pueden ser beneficiosos para contrarrestar la depresión cardiovascular asociada con el bloqueo neurocentral. Se halló un alto grado de eliminación de clorometiazola (media de 1,39 litro min^{-1}, Desviación Típica de 0,58) en el cuerpo y esto contribuiría a la breve duración de la actividad al término de la infusión.

Br. J. Anaesth. (1981), **53**, 1211

AN INTRADERMAL STUDY OF THE LOCAL ANAESTHETIC AND VASCULAR EFFECTS OF THE ISOMERS OF MEPIVACAINE

J. W. FAIRLEY AND F. REYNOLDS

SUMMARY

The duration of action and vascular effects of L(+) and D(−) and racemic mepivacaine were investigated in a double-blind study in 23 fit volunteers. Isosmolar 0.1-ml intradermal injections of a range of concentrations of each agent from 0.011% to 2.7%, and physiological saline were given in duplicate to at least 14 subjects. Local colour changes were observed 5–10 min after injection, and analgesia to pinprick was tested at 5-min intervals thereafter until full recovery. Both isomers were vasoconstrictor at concentrations of 0.3% and less; at greater concentration the L isomer produced more vasodilatation and haemorrhagic change. The duration of action of both isomers increased with concentration between 0.05 and 0.9%, but the L isomer was significantly longer acting than the D at 0.3% and more. The log dose–duration curve could be interpreted as linear between 0.1 and 0.9% with the slope of L isomer being twice as steep as the D. The findings for racemic mepivacaine were between those of the two isomers. The longer duration of analgesia of L-mepivacaine was not associated with superior vasoconstrictor power.

The duration of action of a local anaesthetic is determined by the time for which an effective concentration is maintained within the axonal membranes of pain conducting neurones. Reduction in local blood flow slows the rate of removal and prolongs the action. Because of the disadvantages of adding vasoconstrictors, suitable local anaesthetics with intrinsic vasoconstrictor activity have been sought. Those developed since lignocaine possess an asymmetric carbon atom and exist as two stereoisomers, the L and D forms. The terms L and D denote the spatial configuration of the molecule, while laevo-rotatory (−) and dextrorotatory (+) denote the optical activity, which does not necessarily correspond to spatial configuration and is of little importance biologically. Pairs of isomers have the same physicochemical properties and *in vitro* local anaesthetic potency (Akerman, Persson and Tegner, 1967; Åberg, 1972) and in clinical practice the racemic mixtures are used. However, it has been shown that the L(−) bupivacaine, L(+) prilocaine and L(+) mepivacaine are longer acting than the D isomers *in vivo* (Akerman, Persson and Tegner, 1967; Adler, Adler and Åberg, 1969; Luduena, Bogado and Tullar, 1972). In the case of bupivacaine, intradermal studies in man have shown that only the L isomer has local vasoconstrictor activity (Aps and Reynolds, 1978), and this may explain its longer duration of action. The L isomer of mepivacaine was shown to have greater vasoconstrictor activity than the D isomer on rat portal vein (Åberg and Wahlström, 1972).

The present work investigated the local anaesthetic and vascular effects of mepivacaine and its isomers given intradermally to human volunteers. Because vasoactivity of local anaesthetics has been shown to be concentration-dependent, vasoconstriction occurring at low and vasodilatation at high concentrations (Aps and Reynolds, 1976, 1978), a wide range of concentrations of mepivacaine has been investigated.

METHODS

Solutions

D(−), L(+) and racemic mepivacaine hydrochloride were made up to 2.7% and 0.9% (weight of base/vol.) using 0.9% saline and distilled water so that the resulting solutions were isosmolar with 0.9% saline. Serial dilutions to yield the lower concentrations were made using 0.9% saline. Gas–liquid chromatography was used to check that the concentrations of racemic, D- and L-mepivacaine solutions were equal.

Coded sterile ampoules were made up by passing the solution through a Millipore filter,

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displacing air with nitrogen gas, sealing and autoclaving. A check for leaking ampoules was incorporated into the autoclaving procedure, and any leaky ampoules were discarded.

Subjects

The subjects were 23 fit adults, 13 male and 10 female, age range 19–30 yr. There were two studies involving 14 subjects each; five subjects took part in both studies. One subject was an author (J. W. F.) and the rest medical students and laboratory workers who gave informed consent.

Procedure

In the first study, the concentrations 0.1, 0.3 and 0.9% of D, L and DL (racemic) mepivacaine and 0.9% saline control, were tested. Pairs of 0.1-ml injections of each solution were given intradermally on the flexor surface of the forearms; thus 20 injections were given to each subject. Injections were spaced at 4-cm intervals. The position of each solution on the forearm varied at random between subjects and was not known to either subject or experimenter.

Between 5 and 10 min after the injection, colour change in each bleb was assessed by J. W. F. in all cases, and classified as pale, neutral or pink. From these colour changes, a vasoactivity score for the pair of blebs was calculated as follows:

Colour changes	Vasoactivity score
Both blebs pale	2
One pale, one neutral	1
Both neutral	0
One pink, one neutral	−1
Both pink	−2
(Pink and pale did not occur)	

Haemorrhagic changes (bleeding or bruising) were noted. Ten minutes after injection, then every 5 min for the first hour and every 10 min thereafter until full recovery, analgesia was tested by pricking the central area (0.3 mm diameter) of the bleb with a lancet five times while the subject looked away. The number of times a sharp sensation was felt was recorded for each bleb. The time to 50% recovery for each solution was taken as the time at which the combined sharpness score for the pair of blebs reached 5 out of 10. If this occurred between timing intervals the time to 50% recovery was taken as the mid-point of the interval. If the score was 9 or 10 at the first test, the time to 50% recovery was taken as zero.

Because a clear difference in vasoactivity between the isomers was not demonstrated at the concentrations tested in the first study, in the second study the same procedure was followed using 0.011, 0.033, 0.05, 0.3 and 2.7% solutions of D- and L-mepivacaine, and 0.9% saline. Thus each subject received 22 injections.

RESULTS

Analgesic activity

At concentrations less than 0.1% there was little or no difference between the analgesic activities of the two isomers and saline (fig. 1). At 0.1% there

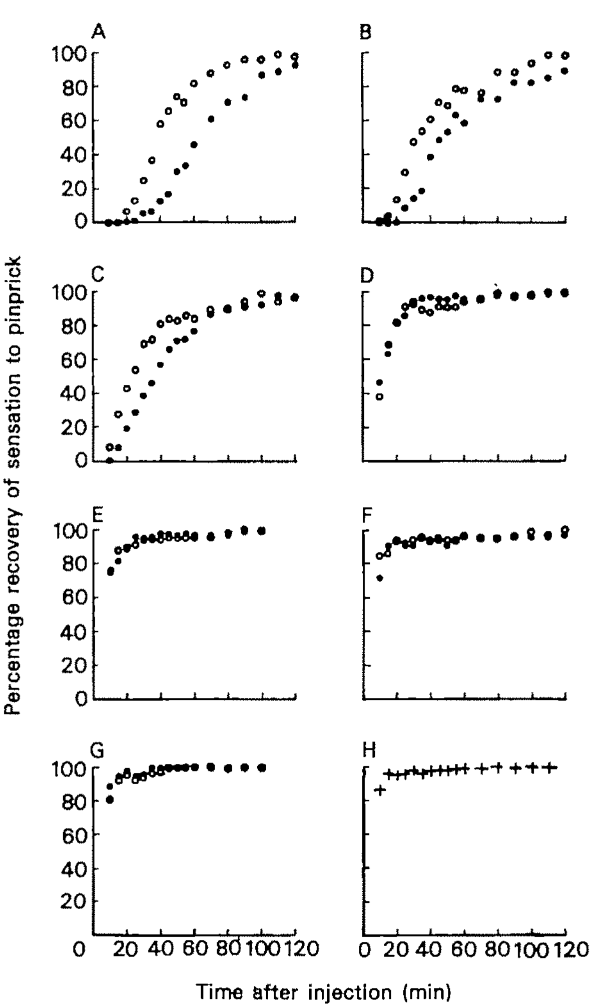

FIG. 1. Mean pinprick scores presented as % of recovery against time for L-mepivacaine (●) and D-mepivacaine (○). A = 2.7%; B = 0.9%; C = 0.3%; D = 0.1%; E = 0.05%; F = 0.033%; G = 0.011%; H = NaCl. n = 14 for each point except NaCl and 0.3%, where n = 28.

was some analgesic activity which wore off within 20 min, but no discernible difference between the isomers. At 0.3, 0.9 and 2.7% concentrations, analgesic activity of the L isomer was greater, the discrepancy between the isomers increasing with concentration. Complete analgesia (0% recovery in all subjects) occurred at 0.3% only with L-mepivacaine, and at higher concentrations lasted longer with L- than with D-mepivacaine.

Duration of action

Recovery was complete or almost so within 2 h after the injection at all concentrations. The times to 50% recovery of all solutions are shown in figure 2. These form sigmoid log dose–duration curves for both the L and D isomers. The duration of action of both isomers was very brief at concentrations up to 0.1%. At higher concentrations, L-mepivacaine was longer acting than D-mepivacaine, and this difference increased with increasing concentration, making the slope of the log dose–duration curve steeper for L-mepivacaine. The upper asymptote of the log dose–duration curve for D-mepivacaine appears to lie at about 40 min, while that for L-mepivacaine is above 70 min. The duration of action of the racemic mixture, over the range of concentrations tested, lies between the two isomers.

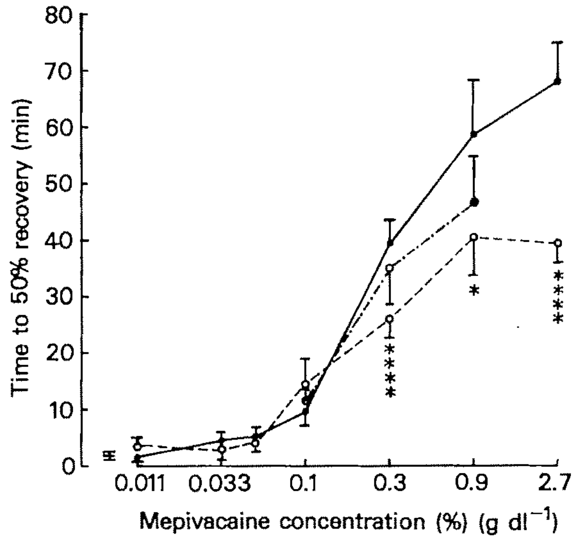

FIG. 2. Mean duration of action for L-mepivacaine (●——●), D-mepivacaine (O--O) and racemic mepivacaine (O-·-O). Vertical bars represent SEM. Differences between L- and D-mepivacaine at given concentrations: *$P<0.05$; ****$P<0.0001$ (paired sample two-tailed t tests).

The central regions of the log dose–duration curves were subjected to analysis of variance using the GLIM3 linear modelling computer program (Baker and Nelder, 1978) which can fit multiple regression lines to the data on the principle of least squares. Linearity of the log dose–duration curves was checked by demonstrating no significant difference in residual variance from a model which allowed curvature. There was considerable inter-subject variation in 50% recovery time, and this was found to be highly significant ($P<0.01$, F test). Subjects appeared to respond to changes in concentration in much the same way, but differed in their susceptibility. This led to the parallel log dose–duration lines model shown in figure 3. However, the slopes did differ between the preparations of L-, D- and racemic mepivacaine (fig. 3D).

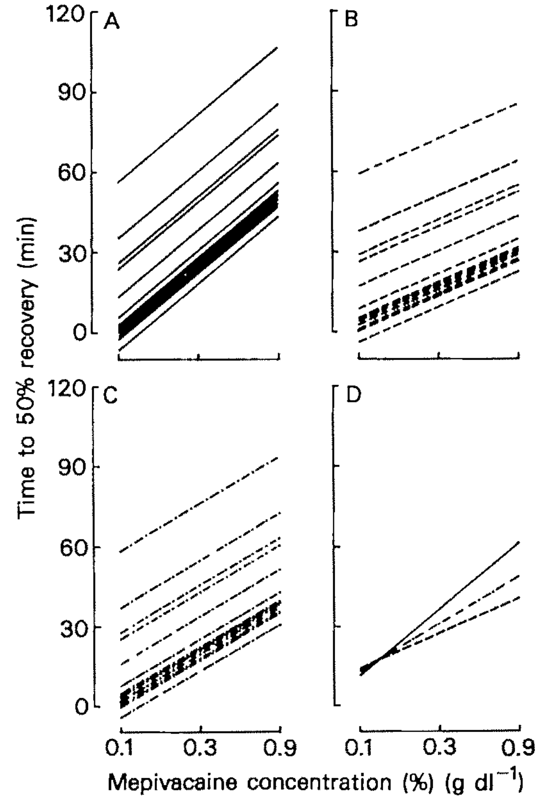

FIG. 3. Time to 50% recovery over middle range of concentrations. Regression lines calculated by GLIM3 linear modelling computer program. Panels A–C = 14 individual lines, taking account of subject variation, for L- (A), D- (B) and racemic (C) mepivacaine. Panel D = mean positions of lines for L-, D- and racemic mepivacaine. Slopes (min per log unit of concentration) (SEM = ±2.58): L, $b = 22.67$; D, $b = 11.87$; DL, $b = 16.01$.

Vascular effects

Vascular effects, as judged by local colour changes, were in all cases transient, and in no case did permanent tissue damage occur. Haemorrhagic changes occurred in 16 of 28 injections of 2.7% L-mepivacaine, and in eight of 28 injections of 2.7% D-mepivacaine. Haemorrhagic changes occurred only four times after the remaining 532 injections, and were apparently unrelated to dose and subject, although all four occurred with L-mepivacaine. The probability of this occurring by chance if the four haemorrhagic changes were equally likely to have been associated with any of the 532 injections is $P = 0.018$.

Vasoactivity varied with concentration as shown in figure 4. Vasodilatation was most frequent at the 2.7% concentration of L-mepivacaine. Comparing the vasoactivity scores within subjects, the vasodilator activity of L-mepivacaine was significantly greater than that of D-mepivacaine at 0.9 and 2.7% concentrations ($P < 0.01$), Wilcoxon's test for pair differences). Both L- and D-mepivacaine showed vasoconstrictor activity which appeared to be maximal at a concentration of 0.1%, but was still significantly greater than that of saline at 0.011% ($P < 0.05$).

No significant difference in vasoconstrictor activity was demonstrated between the L and D isomers at any of the concentrations tested individually, nor taking concentrations 0.011–0.3% as a group, although in four of the five vasoconstrictor concentrations, L-mepivacaine showed greater activity. Racemic mepivacaine produced colour changes similar to those caused by the L isomer.

DISCUSSION

The prolonged duration of action of L- compared with D-mepivacaine confirms the results of other investigations (Adler, Adler and Åberg, 1969; Åberg and Adler, 1970; Åberg, 1972). The sigmoid nature of the log dose–duration curves, the demonstration of a central linear region which varies in slope between isomers, and the existence of different asymptotes for maximal duration of action, show that there is some difference between the pharmacological activity profiles of the two isomers, rather than a general difference in potency which would have resulted in a parallel shift along the log dose axis.

It was postulated earlier that this difference lay in vascular activity, but the present results do not demonstrate a significant difference in vasoconstrictor activity which could account for the differences in duration of action. L-Mepivacaine was shown to be significantly more vasodilator than D-mepivacaine at high concentrations, but this should result in a more rapid washout, unless it is also associated with an increase in capillary permeability, local oedema and hence reduction of capillary circulation. This is known to occur with irritant concentrations of local anaesthetics (Luduena, 1969), and the high frequency of

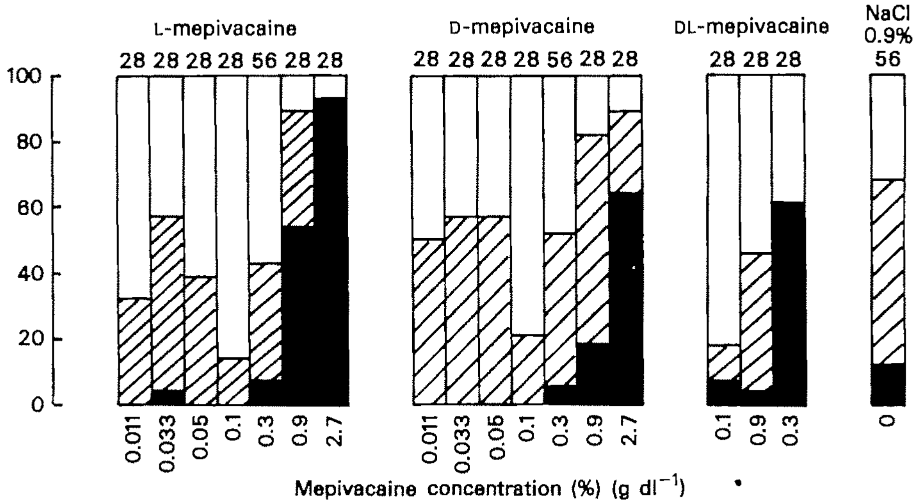

FIG. 4. % Frequency of local colour changes with racemic mepivacaine and its isomers. ■ = pink; ▨ = neutral; □ = pale. The number over each column indicates the total number of injections of that solution.

haemorrhagic changes observed in the present study indicates that 2.7% mepivacaine may produce local irritation (Reynolds, Bryson and Nicholas, 1976) which is more common with the L isomer than with the D.

Comparing figures 2 and 4, it is evident that the occurrence of vasoconstriction does not coincide with maximum analgesic activity, but with lower concentrations. However, in the area around a high concentration, diffusion may produce the lower vasoconstrictor concentrations. This is supported by the fact that pale rings were frequently seen around the pink blebs as time went on. Where pallor (vasoconstriction) occurs at the centre of a bleb, a longer duration of action for a given drug and dose might be expected. This was tested by including the vasoactivity score as a covariate in the log dose–duration model. A small effect in the expected direction was noted, but this was not statistically significant. L- and D-mepivacaine did not differ significantly in this respect. However, there may be factors other than vasoactivity to explain the prolonged duration of action of L-mepivacaine. The rate of diffusion away from the injection site has been shown to be greater for tritiated D- than for L-mepivacaine in guineapig skin (Åberg, 1972), a difference still being present when the effect of capillary circulation washout was eliminated by killing the guineapig just before the injection. It was suggested that the L isomer may undergo greater tissue binding than the D. We carried out some preliminary observations on the oral absorption of the two isomers, using the method of Beckett and Triggs (1967). There was no obvious difference between the two isomers in their percentage absorption by the oral mucosa, over a range of isosmotic pH values from 5.4 to 9.0. Thus, absorption by oral mucosa does not demonstrate the postulated differences in tissue binding, but this may be because such absorption is principally influenced by lipid solubility and pKa.

We have demonstrated a clear difference in duration of action between the isomers of mepivacaine, which conforms with the findings of Luduena, Bogado and Tullar (1972). In the present study this difference increased with concentration, but the longer action of the L isomer was not associated with superior vasoconstrictor powers. This is surprising since, first, Åberg and Andersson (1972) showed that, in low concentration, L-mepivacaine had a contractile effect on rat portal vein while the D isomer caused relaxation. Second, there was a clear distinction between the isomers of bupivacaine when vasoactivity and duration were tested intradermally in man (Aps and Reynolds, 1978) while the distinction was less marked in the rat portal vein (Åberg and Wahlström, 1972).

That both isomers of mepivacaine can produce vasoconstriction accords with the superior vasoconstrictor properties of racemic mepivacaine over other local anaesthetics at concentrations used clinically (Reynolds, 1980).

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ETUDE INTRADERMIQUE DE L'AGENT ANESTHESIANT LOCAL ET DES EFFEFTS VASCULAIRES DES ISOMERES DE LA MEPIVACAINE

RESUME

Nous avons fait des recherches au cours d'une étude à double inconnue portant sur 23 volontaires en bonne santé, pour déterminer la durée d'action et les effets vasculaires de L(+), D(−) et de la mépivacaïne racémique. Des injections isomoléculaires intradermiques de 0,1 ml d'une gamme de concentrations de chaque agent—comprises entre 0,011% et 2,7%—et de soluté physiologique ont été administrées en double à au moins 14 sujets. On a observé des changements de couleur locaux entre 5 et 10 mn après l'injection et l'analgésie à la piqûre d'aiguille a été testée à intervalles de 5 mn tout de suite après et jusqu'à la récupération totale. Les deux isomères ont été vasoconstricteurs aux concentrations de 0,3% et moins; à des concentration plus fortes, l'isomère L a produit davantage de vasodilatation et de changements hémoragiques. La durée d'action des deux isomères a augmenté avec les concentrations se situant entre 0,05% et 0,9%, mais l'isomère L a eu une durée d'action nettement plus longue que D à 0,3% et plus. Le logarithme de la courbe dose-durée peut être interprété comme étant linéaire entre 0,1 et 0,9%, la pente de l'isomère L étant deux fois plus prononcée que D. Les résultats obtenus pour la mépivacaïne racémique se sont situés entre ceux des deux isomères. La durée d'analgésie plus longue de la mépivacaine L n'a pas été associée à une puissance vasoconstrictrive supérieure.

EINE INTRADERMALSTUDIE DER LOKALANÄSTHESIE- UND GEFÄSSWIRKUNGEN DER ISOMERE VON MEPIVACAIN

ZUSAMMENFASSUNG

Wirkungsdauer und Gefässauswirkungen von L(+) und D(−) und von racemischem Mepivacain wurden in einer Doppel blindstudie an 23 gesunden versuchspersonen untersucht. Isosmolar 0,1 ml-Intradermalinjektionen einer Reihe von Konzentrationen eines jeden Mittels, von 0,011% bis 2,7%, sowie eine physiologische Kochsalzlösung wurden im Duplikat an mindestens 14 Versuchspersonen verabreicht. Lokale Farbveränderungen wurden 5–10 Min nach der Injektion beobachtet, und anschliessend wurde die Empfindlichkeit auf Nadelstiche in 5 Min-Intervallen bis zur völligen Erholung getestet. Beide Isomere waren gefässverengend bei Konzentrationen bis zu 0,3%; bei Spitzenkonzentrationen bewirkte das L-Isomer mehr Gefässerweiterung und hämorrhagische Veränderungen. Die Wirkungsdauer beider Isomere stieg bei Konzentrationen zwischen 0,05 und 0,9%, wobei das Gefälle des L-Isomers doppelt so steil war wie das des D-Isomers. Die Ergebnisse für racemisches Mepivacain lagen zwischen denen der beiden Isomere. Die längere Schmerzlinderungsdauer von L-Mepivacain hatte nichts mit einer überlegenen gefässverengenden Kraft zu tun.

UN ESTUDIO INTRADERMAL DE LA ANESTESIA LOCAL Y DE LOS EFECTOS VASCULARES DE LOS ISOMEROS DE LA MEPIVACAINA

SUMARIO

Se investigó la duración de la actividad y los efectos vasculares de L(+) y D(−) y de la mepivacaína racémica, en un estudio de doble anonimato efectuado en 23 voluntarios sanos. Se administraron por duplicado a, por lo menos, 14 sujetos, inyecciones intradermales de 0,1 ml isomolar, en una gama de concentraciones entre 0,011% a 2,7% para cada agente, asi como soluciones salinas fisiológicas. Se observaron combios locales de color despues de los 5–10 min de la inyección y se comprobó la analgesia a los pequeños pinchazos a intervalos de 5 min hasta la recuperación total. A concentraciones de 0,3% e inferiores, ambos isómeros fueron vasoconstrictores; a la máxima concentración el isómero L produjo una mayor vasodilatación y un mayor cambio hemorrágico. La duración de la actividad de ambos isómeros aumentó con la concentración, entre 0,05 y 0,9%, pero la actividad del isómero L fue significativamente de mayor duración que la del D a concentraciones de 3% y de valores superiores. La curva logarítmica de dosis–duración podria interpretarse como lineal entre 0,1 y 0,9%, siendo la pendiente del isómero L doble que la del D. Los resultados para la mepivacaína racémica quedaron comprendidos entre los de los dos isómeros. La mayor duración analgésica de la mepivacaína L no vino asociada con una potencia vasoconstrictora superior.

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TEMPERATURE DEPENDENCE OF MUSCLE FUNCTION IN MALIGNANT HYPERPYREXIA-SUSCEPTIBLE SWINE

J. S. SULLIVAN AND M. A. DENBOROUGH

SUMMARY

Contractures induced by halothane, caffeine, suxamethonium chloride and potassium chloride in malignant hyperpyrexia-susceptible (MHS) and control swine skeletal muscle preparations were temperature-dependent, but differed in their temperature response profiles. Increasing the temperatures from 20 °C to 37 °C increased drug-induced contractures in MHS muscle. At 5 °C drug-induced contractures were not inhibited by dantrolene sodium, deuterium oxide or glycerination in either MHS or control muscle. These observations give further support to the view that the abnormality in MHS skeletal muscle is associated with the mechanism of excitation–contraction coupling.

Malignant hyperpyrexia (MH) occurs in individuals who have an underlying disease of muscle (Denborough, 1980). A similar condition has been described in certain breeds of swine, including Landrace, Pietrain and Poland China breeds (Campion and Topel, 1975). *In vitro* studies on susceptible human (Moulds and Denborough, 1974) and swine skeletal muscle (Okumura, Crocker and Denborough, 1979) have shown that when MHS muscle is exposed to certain anaesthetic agents a contracture of the muscle occurs. This reflects the high myoplasmic calcium concentrations produced by the precipitating agents, but the precise nature of the skeletal muscle abnormality remains to be identified.

The initial report of enhanced contractures to caffeine in MHS human muscle was an important development in the pharmacological identification of the skeletal muscle abnormality (Kalow et al., 1970). Although halothane contractures were not observed in this investigation, later studies showed spontaneous contractures on exposure of MHS muscle to halothane (Ellis et al., 1972; Moulds and Denborough, 1972). This discrepancy was subsequently explained when halothane-induced contractures in MHS muscle were found to be temperature-dependent (Nelson, Bedell and Jones, 1975).

The present investigation examines in detail the effects of temperature on MHS swine skeletal muscle with the aim of obtaining additional information on the processes modulating muscle contractile hypersensitivity in MH.

MATERIALS AND METHODS

Muscle biopsy was performed in fourteen MHS and three control swine. In all cases susceptibility was assessed by pharmacological methods (Okumura, Crocker and Denborough, 1979). Anaesthesia was carried out as described previously (Okumura, Crocker and Denborough, 1979), with the exception that the neuroleptanalgesic azaperone (Stresnil) was used for premedication (4 mg kg^{-1}). The composition of the Ringer buffer and the procedures involved in the preparation of the muscle fibres have also been described previously (Moulds and Denborough, 1974).

Fibre bundles were stimulated with a 3-ms, 30-V pulse at 10-s intervals using a resting tension of 1 g. The stock solutions of the drugs used were caffeine 100 mmol litre^{-1} in Ringer, potassium chloride 4 mol litre^{-1} in Ringer, suxamethonium chloride 125 mmol litre^{-1} in distilled water, tubocurarine 1.47 mmol litre^{-1} in distilled water and dantrolene sodium 3 mmol litre^{-1} in dimethyl sulphoxide. Halothane was administered by passing 5% carbon dioxide in oxygen (carbogen) through a temperature-calibrated Dragewick vaporizer. Glycerinated muscle fibres and the deuterium oxide (D_2O) Ringer were prepared and used as described previously (Okumura, Crocker and Denborough, 1980).

Temperature control was maintained with a Braun thermomix equipped with a mercury

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contact thermometer. In experiments designed to follow twitch responses to a gradual increase in temperature, the temperatures in the circulating water bath and in the buffer were monitored separately. Muscle fibres were first equilibrated at 5 °C and the final temperature was set at 37 °C. This resulted in an increase in temperature in the buffer of 2.5 °C min^{-1}. A total of seven control and 12 MHS fibre preparations was used, with a maximum of three from any individual animal. The twitch responses at a given temperature were calculated as a percentage of the maximum twitch obtained.

For fixed temperature experiments in the 20–45 °C range, the circulating water bath temperature was set, and the buffer temperature was allowed to equilibrate to the pre-set value before the muscle fibres were transferred to the organ bath. The buffer temperature was maintained to within ±0.5 °C of the desired temperature. The 5 °C temperature was maintained by the addition of ice to the circulating water bath. Only one fibre preparation per animal was used at each different temperature.

Statistical methods

The differences in twitch responses between MHS and control muscle were analysed statistically using Student's *t* test.

The differences in drug-induced contractures in MHS muscle at different temperatures were also analysed statistically by Student's *t* test, using 37 °C as the reference temperature.

RESULTS

Recovery of isometric twitch occurred at a lower temperature in MHS muscle than in control muscle (fig. 1). The temperature at which maximum twitch occurred was also significantly less ($P < 0.05$) in MHS (21.2 ± 0.8 °C, $n = 12$) than in control muscle (24.1 ± 0.7 °C, $n = 7$). Tubocurarine pretreatment (final concentration 0.06 mmol litre^{-1}) did not alter the temperature twitch response pattern in MHS ($n = 3$) or control ($n = 3$) fibres.

Similar temperature contracture profiles were obtained in MHS fibres in response to 3% halothane (fig. 2), caffeine 2 mmol litre^{-1} (fig. 3) and suxamethonium chloride 1 mmol litre^{-1} (fig. 4) with maximum and minimum contractures occurring at 5 °C and 25 °C respectively. Potassium chloride 80 mmol litre^{-1} induced maximum contractures at 37 °C and there was a marked decrease in contractures on either side of this temperature (fig. 5)

Prior glycerination at 37 °C or the replacement of the normal Ringer buffer with a deuterium oxide-based buffer had no effect on 5 °C contractures induced by halothane, caffeine or suxamethonium chloride in either MHS or control fibres ($n = 3$, for all treatments in each group). Dantrolene sodium 12 µmol litre^{-1} did not inhibit

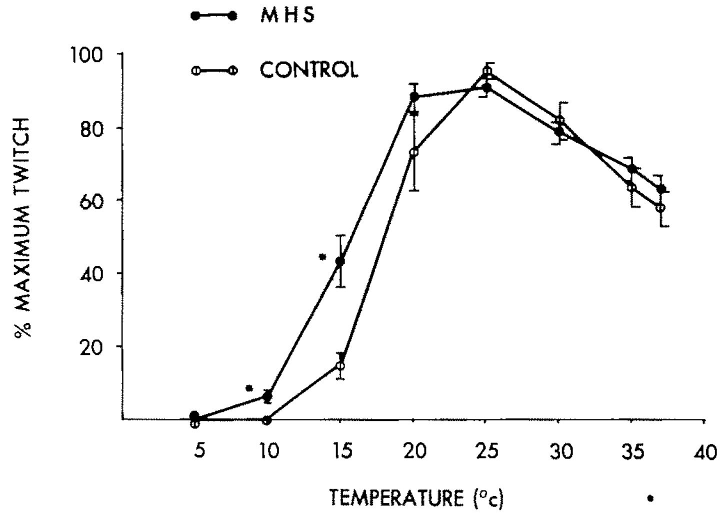

FIG. 1. The effect of temperature on isometric twitch in MHS and control swine gracilis muscle. Mean ± SEM of 12 and seven fibre preparations from five MHS and three control swine respectively. *$P < 0.05$.

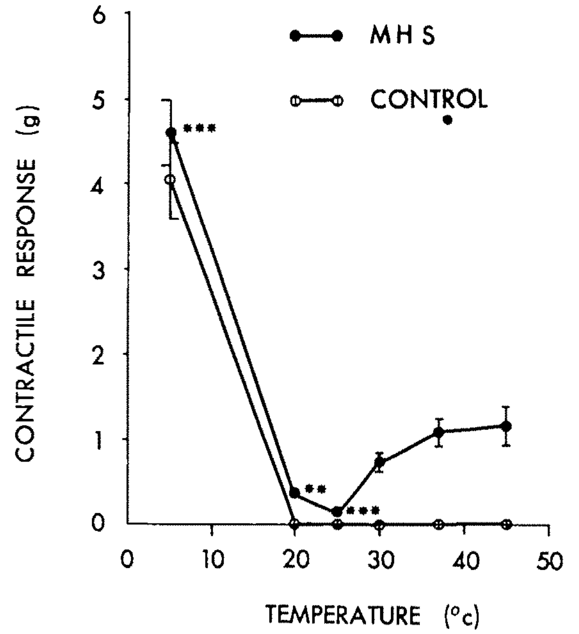

FIG. 2. Temperature dependence of 3% halothane-induced contractures in MHS and control swine gracilis muscle. Mean ± SEM of 7–14 MHS and three control fibre preparations. P values refer only to MHS muscle, using 37 °C as the reference temperature. $^{**}P<0.01$; $^{***}P<0.001$.

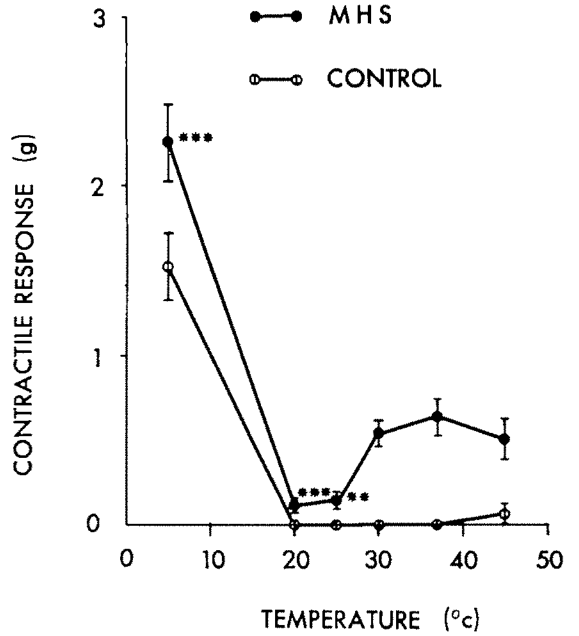

FIG. 3. Temperature dependence of contractures induced by caffeine 2 mmol litre^{-1} in MHS and control swine gracilis muscle. Mean ± SEM of 7–14 MHS and three control fibre preparations. The P values refer only to MHS muscle, using 37 °C as the reference temperature. $^{**}P<0.01$; $^{***}P<0.001$.

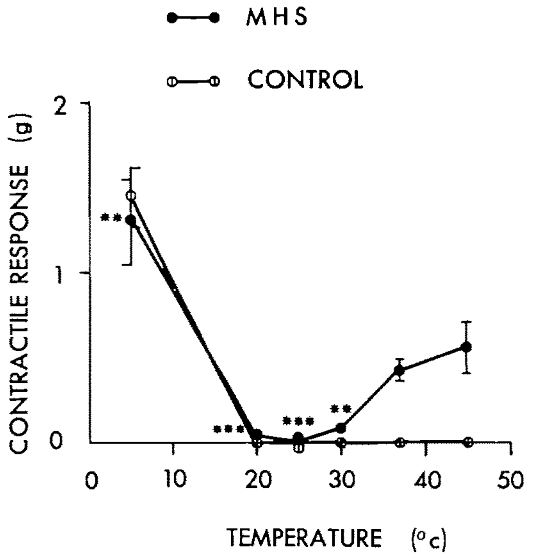

FIG. 4. Temperature dependence of contractures induced by suxamethonium chloride 1 mmol litre^{-1} in MHS and control swine gracilis muscle. Mean ± SEM on 7–14 MHS and three control fibre preparations. P values refer only to MHS muscle, using 37 °C as the reference temperature. $^{**}P<0.01$; $^{***}P<0.001$.

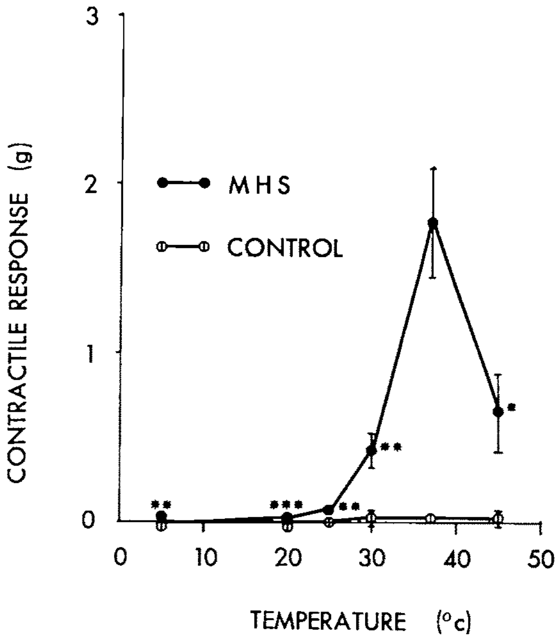

FIG. 5. Temperature dependence of contractures induced by potassium chloride 80 mmol litre^{-1} in MHS and control swine gracilis muscle. Mean ± SEM of 7–14 MHS and three control fibre preparations. P values refer only to MHS muscle, using 37 °C as the reference temperature. $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

halothane or caffeine contractures at 5 °C ($n = 3$, for each treatment in MHS and control muscle). Repeated drug contractures in a calcium-free buffer at 5 °C markedly reduced halothane and caffeine contractures in MHS ($n = 3$) and control ($n = 3$) fibre preparations.

The pH of the buffer solution was measured at all the temperatures. At 5 °C the pH of the buffer solution decreased to 6.9. Restoring the pH of the buffer to 7.4 by increasing the bicarbonate concentration (Creese, Scholes and Taylor, 1958) had no effect on the halothane- or caffeine-induced muscle contractures at 5 °C.

DISCUSSION

The increase in twitch shown by MHS swine gracilis muscle (fig. 1) on decreasing temperature from 37 °C to 20 °C, contrasts with the decreased contractile responses to halothane, caffeine, suxamethonium chloride and potassium chloride over the same temperature range. A similar effect has been described in rat extensor digitorum longus muscle where twitch increases (Close and Hoh, 1968) and caffeine contractures decrease (Frank and Buss, 1967) as temperatures are decreased from 37 °C to 20 °C. As the final events in contraction are common to both twitch- and drug-induced contraction (calcium release and myofibrillar interdigitation), an explanation for their different temperature sensitivities may lie in the sequence of events occurring before calcium release.

The inability of the acetylcholine antagonist tubocurarine of modify either the recovery or the pattern of twitch as a function of temperature, argues against acetylcholine release and the motor end-plate being responsible for the temperature–twitch profile displayed by porcine gracilis muscle.

Biochemical studies in isolated rat (Becker and Willis, 1975) and porcine (McIntosh, Berman and Kench, 1977) sarcoplasmic reticular preparations have shown that Ca^{2+} ATPase activity decreases as temperatures are decreased from 37 °C to 20 °C. Thus a decrease in calcium uptake may cause the greater twitch in MHS and control muscles in the 20–25 °C temperature range, but this cannot explain the loss of drug-induced contractures that occurred over the same temperature range in MHS muscle.

The decreased drug-induced contractures found in MHS muscle on reducing temperature from 37 °C to 25 °C suggest that the hypersensitive step coupling excitation to subsequent calcium release has been dissociated, and it is proposed that this site is localized at the level of the functional interaction between the T-tubule and the sarcoplasmic reticulum. It is possible that the hypersensitive drug-induced contractures which occur in MHS muscle at 37 °C may reflect the ability of such drugs (halothane, caffeine and suxamethonium chloride) to initiate calcium-induced calcium release (Endo, 1977; Ebashi, 1979), a process which does not occur in normal muscle.

Calcium uptake by rabbit sarcoplasmic reticular fragments is abolished at 2 °C (Martonosi and Feretos, 1964), suggesting that the large drug contractures induced at 5 °C may reflect a decrease in the ability of swine sarcoplasmic reticulum to accumulate calcium. The calcium-dependence of the 5 °C drug contractures was illustrated by their diminution with repeated drug treatments in calcium-free Ringer. The disappearance of twitch and the loss of potassium chloride-induced contractures at 5 °C imply a loss of surface excitability, and it is possible that halothane, caffeine and suxamethonium chloride induce muscle contractures at 5 °C by a direct action on sarcoplasmic reticular stores of calcium. The similarity between the degree of contracture induced by these drugs at 5 °C in MHS and control muscle indicates that under these conditions the amount of calcium released does not differ between the two muscle preparations.

The rapid cooling contracture (RCC) which occurs in frog muscle in response to caffeine, at concentrations which constitute sub-threshold contractile doses at room temperature (Conway and Sakai, 1960), is similar to the low temperature contractures studied in the present investigation. There is a difference in the temperature procedures used, as the caffeine RCC technique involves the rapid transfer of muscle from a 20 °C buffer to one maintained at 0 °C (Conway and Sakai, 1960), while the fixed temperature method used in the present study allows equilibration at 5 °C before the addition of any drug. An additional difference is the reported ability of dantrolene to inhibit caffeine RCC in frog muscle (Homma, Kurihara and Sakai, 1976), compared with the inability of dantrolene to block halothane or caffeine-induced contractures in porcine muscle at 5 °C in the present investigation.

The inability of a variety of excitation–contraction uncoupling treatments to modify halothane-, caffeine- or suxamethonium chloride-induced contractures at 5 °C suggests that membrane excitability is not a requirement for such low-temperature contractures, and is further evidence for a direct action of these drugs on the sarcoplasmic reticulum to induce calcium release.

The optimal temperature at which to assess MH susceptibility by *in vitro* pharmacological methods has been suggested to be 37 °C (Denborough, 1980). This conclusion has been reached in studies of pig muscle (Nelson, Bedell and Jones, 1975), and of caffeine-induced contractures in control human muscle (Nelson, Austin and Denborough, 1977). In the present study a detailed assessment of *in vitro* drug-induced contractures in MHS skeletal muscle over a range of temperatures gives further support to the view that *in vitro* pharmacological assessment of MH susceptibility should be carried out at 37 °C.

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DEPENDANCE SUR LA TEMPERATURE DE LA FONCTION MUSCULAIRE DANS L'HYPERPYREXIE MALIGNE DE PORCS SUJETS A CETTE MALADIE

RESUME

Les contractions induites par l'halothane, la caféine, le chlorure de suxaméthonium et le chlorure de potassium sur des préparations de muscle strié de porcs sujets à l'hyperpyrexie maligne (MHS) et leur contrôle ont été fonction de la température, mais ont différé dans les profils de leur réaction à la température. Lorsqu'on a fait passer la température de 20 °C à 37 °C, on a augmenté les contractions produites par le médicament sur le muscle MHS. A 5 °C, ces contractions n'ont pas été inhibées par le dantrolene sodium, l'oxyde de deutérium ou la glycérination dans le muscle MHS ou dans le muscle témoin. Ces observations confirment le point de vue que l'anomalie dans le muscle strié MHS est associée au mécanisme de couplage excitation/contraction.

DIE TEMPERATURABHÄNGIGKEIT VON MUSKELFUNKTIONEN BEI SCHWEINEN, DIE GEGEN BÖSARTIGE HYPERPYREXIE ANFÄLLIG SIND

ZUSAMMENFASSUNG

Kontrakturen, die durch Halothan, Koffein, Suxamethoniumchlorid und Kaliumchlorid in bösartigen hyperpyrexie-anfälligen und kontrollschwein-Skelettmuskel-

präparaten waren temperaturabhängig, zeigten aber unterschiedliche Reaktionen auf Temperatur. Beim Steigern der Temperatur von 20 °C auf 37 °C nahmen drogeninduzierte Kontrakturen in bösartigen hyperpyrexie-anfälligen Muskeln zu. Bei 5 °C wurden drogeninduzierte Kontrakturen weder in bösartigen hyperpyrexie-anfälligen Muskeln noch in Kontrollmuskeln gehemmt, und zwar weder durch Dantrolennatrium, noch durch Deuteriumoxyd oder Glyzerination. Diese Beobachtungen unterstützen weiter die Ansicht, dass das Abnormale bei bösartigen hyperpyrexie-anfälligen Skelettmuskeln mit dem Mechanismus der Verkupplung von Reizung und Kontraktion in Verbindung steht.

FUNCIONAMIENTO MUSCULAR Y SU DEPENDENCIA DE LA TEMPERATURA EN CERDOS SUSCEPTIBLES DE HIPERPIREXIA MALIGNA

SUMARIO

Las contracciones musculares inducidas por las preparaciones de halotano, cafeína, cloruro de suxametonio y de cloruro de potasio en los músculos del esqueleto de los cerdos de control y de los susceptibles a la hiperpirexia maligna (MHS) demostraron ser dependientes de la temperatura, pero difirieron en las características de dicha respuesta a la temperatura. El incremento de las temperaturas desde 20 °C a 37 °C produjo un incremento de las contracciones inducidas por la droga en aquellos músculos MHS. A 5 °C las contracciones inducidas por la droga no quedaron inhibidas mediante el dantroleno de sodio, el óxido de deuterio ni por la glicerinización, ni en músculo de control ni en el de MHS. Estas observaciones apoyan complementariamente el punto de vista de que la abnormalidad en el músculo MHS del esqueleto viene asociada con el mecanismo del par de excitación-contracción.

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ELECTROMANOMETRIC CONFIRMATION OF NEEDLE POSITION IN HAEMOPERICARDIUM WITH SEVERE TAMPONADE

J. ZATTONI, C. SIANI AND B. PERRIA

SUMMARY

Simultaneous recording of the electrocardiogram and of the pressure transmitted through the drainage needle in patients with haemopericardium provided confirmation that the needle tip was in the pericardial cavity. Proper position was indicated by a positive pressure wave beginning before the QRS complex, reaching its maximum value in the first part of the ST segment and ending with the T wave. In contrast, ventricular penetration was signalled by a positive pressure wave beginning in the first part of the QRS complex, reaching its maximum during the T wave and ending between the T and P waves.

Blind needle introduction to drain haemopericardium is not usually difficult (Stein, Shubin and Weil, 1973; De Quirot et al., 1974). The needle is introduced between the xiphoid process and the left costal margin and directed toward the right shoulder at an angle of 30° to the skin. An alternative approach is to insert the needle at the fifth intercostal space on the left, directed toward the upper dorsal spine. The appearance of blood through the needle indicates that the pericardial cavity has been penetrated.

If the blood is pulsating, it is necessary to ensure that the ventricle has not been punctured. It is taught that a strong or a feeble pulsation indicates ventricular or pericardial puncture respectively. However, this does not apply to patients with severe tamponade associated with marked arterial and ventricular hypotension.

Electrocardiographic monitoring of the needle during its introduction can be useful to establish the position of the needle tip (Stein, Shubin and Weil, 1973). Pericardial penetration is indicated by a sharp increase in the QRS voltage. Ventricular or atrial ectopic beats suggest contact with the epicardium.

We sought a rapid, qualitative and safe method for determining needle position. The working hypothesis was that ventricular systole induces a transient negative pressure wave in and around the pericardial space.

METHODS

Five dogs (20–23 kg) were anaesthetized with ketamine i.m. and thiopentone sodium i.v. After endotracheal intubation, facilitated with suxamethonium, anaesthesia was maintained with a mixture of 70% nitrous oxide, 30% oxygen and 1% enflurane with intermittent positive pressure ventilation of the lungs.

The thorax was opened to expose the pericardium. Catheters of 1.5 mm i.d. were inserted to the tracheal tube and to the pericardial cavity for the recording of the airway and pericardial (PP) pressures. A similar catheter was introduced to the right ventricle via the atrium in four dogs for the recording of the ventricular pressure (VP). During this procedure, one dog exhibited severe cardiac arrhythmia and was withdrawn from the study.

In the other four animals, the catheters were connected to pressure transducers (Statham P 23 AC) and the pressure changes were simultaneously recorded, by means of an ink-writing polygraph (Grass D 5), together with the e.c.g. An extracorporeal reservoir containing isotonic saline was connected to the pericardial cavity through a catheter of 4 mm i.d. affording controlled volume changes of the pericardial fluid.

RESULTS

No pressure could be recorded from the empty pericardial cavity. Following the introduction of saline 50 ml, the basal pressure was 5–8 cm H_2O with two types of oscillation: a wide oscillation reflecting airway pressure; two low pressure waves (a and b, fig. 1) occurring with every cardiac cycle.

Gradual introduction of an additional saline 50–60 ml to the pericardial cavity increased basal

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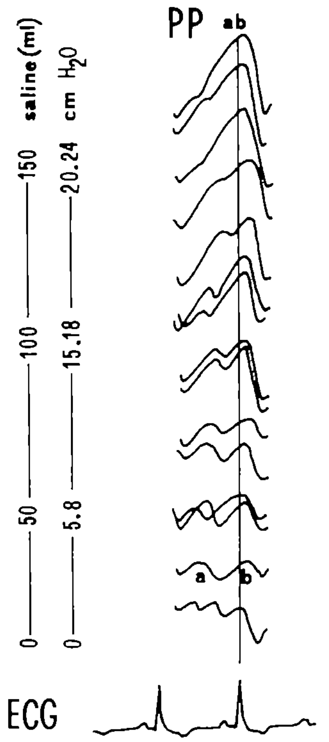

FIG. 1. Three anaesthetized animals receiving intermittent positive pressure ventilation. Pericardial pressure increased from 0 to 20–24 cm H_2O by introducing about 150 ml of saline to the pericardial cavity: a and b, ab PP indicate the cardiogenic pericardial pressure waves associated with the cardiac cycle, represented here by the e.c.g. Note the a and b wave transformation to the ab wave as the basal pericardial pressure was increased to greater than 15 cm H_2O and the sharp reduction of the b or ab pressure waves during the ST segment and the T wave.

PP to greater than 15 cm H_2O. That pressure increase was associated with the transformation of the a and b waves into a single ab wave of the same global duration (fig. 1). The ab wave persisted with the further addition of saline 50–60 ml, resulting in a baseline increase to 20–24 cm H_2O.

In one dog the cyclic respiratory increase of PP was sufficient to cause the periodic transformation of the a and b waves into the ab wave and *vice versa* in spite of there being only 70 ml of saline in the pericardial cavity. In this dog the thorax was temporarily closed and the tidal volume increased to facilitate the wave transformation (fig. 2).

The following relationships were found between cardiogenic pressure waves (a, b and ab) of PP and the e.c.g. waves (fig. 1): (i) The rising phase of a and of ab began immediately after the T wave when VP was at its lowest value. (ii) The rising phase of b started with the P wave and before the systolic increase of the VP. (iii) The falling phase of a ended before the appearance of the P wave. (iv) The falling phase of ab and b started during the ST segment at the moment of the highest value of the VP and ended during the T wave.

DISCUSSION

The intermittent increases of PP attributable to respiratory fluctuations and parallel to events recorded in BAP can be discounted. Endothoracic pressure change during IPPV is well known (Spalding and Smith, 1963) and can be found in all low-resistance structures such as venous and

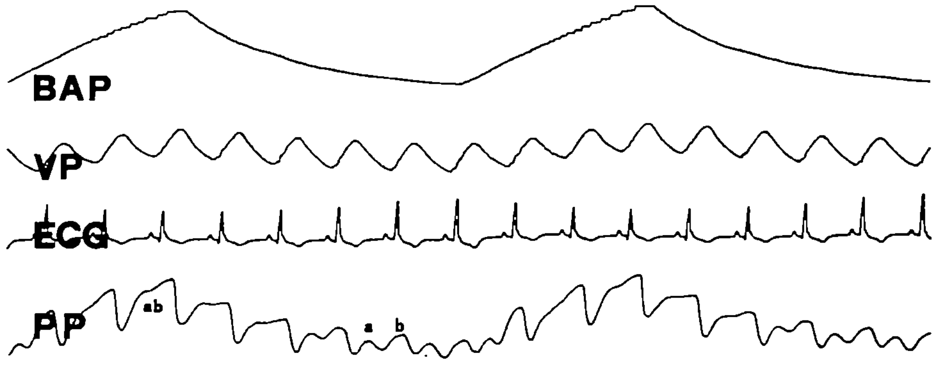

FIG. 2. Animal under general anaesthesia and intermittent positive pressure ventilation: BAP, VP and PP indicate the bronchoalveolar, ventricular and pericardial pressures, respectively. The respiratory PP oscillation was so great that only 70 ml of saline in the pericardium induced all the PP responses to the cardiac cycle.

capillary beds, oesophagus, cardiac atria, mediastinum and pleural space. Our data indicate they reach the cardiac surface, contributing to its tamponade.

PP changes coupled to the cardiac cycle are relevant to our inquiry. These are drawn in figure 3 using the e.c.g. as a common reference to other events (Hamilton, 1962; Ruch and Fulton, 1962; Werkö, 1962; Keele and Neil, 1966).

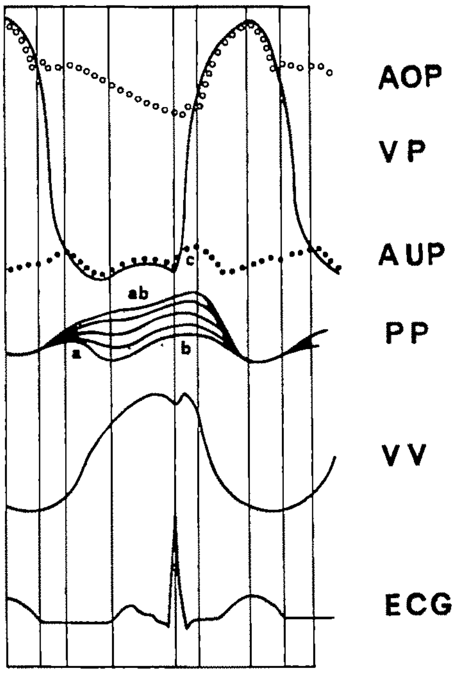

FIG. 3. Relationship of the pericardial pressure changes (PP), as recorded in our experiment with some haemodynamic events of the cardiac cycle: the aortic (AOP), ventricular (VP), atrial (AOP) pressures and the ventricular volume (VV) changes (Hamilton, 1962; Ruch and Fulton, 1962; Werkö, 1962; Keele and Neil, 1966). The e.c.g. is used as a common time axis.

The PP began to increase during the initial phase of ventricular diastole, because of rapid ventricular relaxation. Immediately following this, the increase may lessen or there may be a decrease, the pressure waveform assuming all intermediate shapes between a and b and ab. These different responses to the same cardiac events are because pericardial tension increases from one pattern to the other. Rapid ventricular relaxation and its slower filling produce two separate events when the pericardium is relaxed, the a wave being mainly dynamic. There is a continuous PP increase (ab wave) when pericardial tension is high. The end-diastolic atrial filling could contribute in part to the final increase of PP.

The rapid decrease of PP at the beginning of the isotonic ventricular contraction, because of a sudden decrease of the cardiac volume, can indicate correct needle position; there should be no confusion with other cardiac pressure events. Frequently the c wave is absent (Werkö, 1962) and the atrial hypertension during cardiac tamponade (De Quirot et al., 1974) must be partly responsible. The final decrease of PP begins during the ST segment and ends during the T wave; its previous rising phase precedes the QRS complex. The c wave starts with this complex and its decreasing phase, attributed to ventricular emptying and lowering of the atrioventricular ring (Gordon, 1966), ends during the ST segment. Careful needle placement should make atrial penetration highly unlikely.

Confirmation of our experimental data has been obtained in a patient with mild signs of cardiac tamponade. The gradual evacuation of 750 ml of blood reduced the basal PP from 13 to about 0 cm H_2O. An ab wave was recorded above 8 cm H_2O, at which point it assumed the a and b wave configuration. However, the less the basal PP the more evident was the background pressure noise from patient movement, cough, and irregular breathing. In this condition it can be useful to average the PP signal, taking the Q wave as a triggering stimulus.

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CONFIRMATION ELECTROMANOMETRIQUE DE LA POSITION D'UNE AIGUILLE DANS UN HEMOPERICARDE LORS D'UN EPANCHEMENT GRAVE DE LA CAVITE PERICARDIQUE

RESUME

L'enregistrement simultané d'un électrocardiogramme et de la pression transmise par l'intermédiaire de l'aiguille de drainage sur des patients souffrant d'un hémopéricarde a permis de confirmer que la pointe de l'aiguille se trouvait dans la cavité péricardique. Son emplacement exact a été indiqué par une onde de pression positive commençant avant le complexe QRS, atteignant sa valeur maximale dans la première partie du segment ST et finissant avec l'onde T. Par contraste, la pénétration ventriculaire a été signalée par une onde de pression positive commençant dans la première partie du complexe QRS, atteignant son maximum pendant l'onde T et finissant entre les ondes T et P.

ELEKTROMANOMETRISCHE BESTÄTIGUNG DER NADELPOSITION BEI HERZBEUTELBLUTUNG MIT SCHWERER TAMPONADE

ZUSAMMENFASSUNG

Gleichzeitige Aufzeichnungen von Elektrokardiogramm und des Druckes, der durch die Dränagenadel bei Patienten mit Herzbeutelblutung übermittelt wird, bestätigten, dass sich die Nadelspitze in der Perikardialhöhle befand. Die rechtige Lage wurde durch eine vor der QRS-Gruppe beginnende positive Druckwelle angezeigt, die ihren Maximalwert im ersten Teil des ST-Segments erreichte und mit der T-Welle endete. Im Gegensatz dazu wurde eine ventrikuläre Durchdringung durch eine positive Druckwelle angezeigt, die im ersten Teil der QRS-Gruppe begann, ihr Maximum während der T-Welle erreichte und zwischen der T- und der P-Welle endete.

CONFIRMACION ELECTROMANOMETRICA DE LA POSICION DE LA AGUJA EN EL HEMOPERICARDIO CON TAPONAMIENTO

SUMARIO

El registro simultáneo del electrocardiograma y de la presión transmitida a través de la aguja de drenaje colocada en pacientes con hemopericardio, proveyó la confirmación de que la punta de la aguja se encontraba en la cavidad pericardial. La posición apropiada se indicó mediante una onda de presión efectiva que comenzó antes del complejo QRS, alcanzó su valor de cresta durante la primera parte del segmento ST y terminó con la onda T. Por el contrario, la penetración ventricular se indicó mediante una onda de presión efectiva que comenzó en la primera parte del complejo QRS, alcanzó su valor de cresta durante la onda T y terminó entre las ondas T y P.

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EFFECTS OF NITROUS OXIDE AND OXYGEN ON TRACHEAL TUBE CUFF GAS VOLUMES

S. MEHTA

SUMMARY

The changes in the volume of the cuffs of 200 air-inflated tracheal tubes were studied on exposure to 70% nitrous oxide and 30% oxygen. The length of the cuff, its diameter, wall thickness and residual volume were measured. Increases in the volume of gas occurred in all tubes in a time-dependent manner. The tracheal tubes with low-pressure cuffs were more permeable to nitrous oxide and oxygen than those with high-pressure cuffs. Implications of these findings and the factors which govern the transmission rates of gases through cuff material are discussed.

In vitro studies and investigations in patients have shown that nitrous oxide and oxygen diffuse into air-inflated cuffs of tracheal tubes, thereby increasing their volume and pressure (Stanley, 1974, 1975; Revenäs and Lindholm, 1976; Bernhard et al., 1978). Overinflation of the cuff on the tracheal tube, secondary to the diffusion of nitrous oxide may lead to sore throat, glottic and sub glottic oedema and erosion of the tracheal mucosa. This study was undertaken to measure the changes in the volume of the cuff which occur during exposure to a nitrous oxide–oxygen gas mixture and to compare the physical characteristics of the cuffs of tracheal tubes used commonly in the United Kingdom.

MATERIALS AND METHODS

The permeability of the cuffs of tracheal tubes to nitrous oxide and oxygen was studied in two types of tracheal tube. Group I consisted of tubes with low-pressure cuffs: Portex Profile, Searle Medical Sensiv and Mallinckrodt hi-lo. Group II contained tubes with high-pressure cuffs: Magill red rubber and Leyland Cuftrac latex. Forty tracheal tubes of each type were tested; 20 tubes of 9.0 mm i.d. and 20 of 8 mm i.d.

The 200 cuffed tracheal tubes were placed, in lots of 10, into a 6.5-litre capacity glass environmental chamber at approximately 1 atmosphere pressure. After complete deflation the cuffs were inflated with 10 ml air and exposed to a continuous flow of 5 litre min^{-1} of 70% nitrous oxide and 30% oxygen for periods of 1, 2 and 3 h. The volume of gas in the cuff was measured at the end of these periods with a calibrated and lubricated 10-ml glass syringe using a three-way stopcock. Syringes and stopcocks were tested for leaks using a 20-s compression test before each investigation. The gas volumes withdrawn from the cuffs were measured at atmospheric pressure and at room temperature. All the investigations were performed at 21 °C and approximately 50% relative humidity.

The length, wall thickness, residual volume and diameter of 20 selected cuffs of each type were determined. Length and diameter were measured at residual volume with a Vernier caliper. The residual volume of the cuff was determined by connecting each tracheal tube cuff *via* a three-way stopcock to a 10-ml calibrated glass syringe. The residual volume of the cuff was defined as the maximum volume of air which could be introduced into an empty cuff while maintaining the pressure in the cuff at 1 atmosphere. A micrometer with friction thimble for standardization of measuring force was used to measure the thickness of the cuff.

RESULTS

The exposure to the mixture of 70% nitrous oxide in oxygen resulted in a time-dependent increase in the volume of gas in the cuffs of all tubes (tables I–IV). The largest absolute change in gas volume occurred, in all the tubes, during the 1st hour. After 1 h the continued exposure to this gas mixture resulted in small but steady increases in the volume of gas in the cuffs.

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TABLE I. *Effects of nitrous oxide–oxygen (70–30%) on the gas volumes (mean ± SD) in the cuffs of low-pressure tracheal tubes filled initially with 10 ml of air*

Tracheal tube	Size	Increase in cuff volume (ml)		
		1 h	2 h	3 h
Portex Profile	8 mm	4.5±0.63	5.52±0.49	7.37±0.64
	9 mm	4.9±0.57	6.87±0.76	7.85±0.46
Searle Sensiv	8 mm	5.3±1.80	7.50±1.90	10.35±1.10
	9 mm	6.6±0.62	8.76±0.84	11.70±1.06
Mallinckrodt hi-lo	8 mm	6.5±0.40	9.70±0.70	12.60±0.70
	9 mm	6.8±0.62	10.00±0.87	12.73±0.82

The tracheal tubes with low-pressure cuffs were more permeable to nitrous oxide and oxygen than those with high-pressure cuffs. The mean change in the volume of the cuff in Mallinckrodt hi-lo tubes and Searle Sensiv tubes was greater than that in Portex Profile tubes at 1, 2 and 3 h (table I). After 3 h exposure the increases in volume with 9.0-mm Mallinckrodt hi-lo, Searle Sensiv and Portex Profile tubes averaged 127, 117 and 78% respectively and with 8.0-mm Mallinckrodt hi-lo, Searle Sensiv and Portex Profile 126, 103 and 73% respectively (fig. 1).

In the group containing tracheal tubes with high-pressure cuffs, Leyland Cuftrac latex tubes were more permeable to nitrous oxide and oxygen than Magill red rubber (table II). After 3 h exposure the increases in gas volume in 9.0-mm Leyland Cuftrac latex tubes and Magill red rubber averaged 60 and 47% respectively and in 8.0-mm Leyland Cuftrac latex tubes and Magill red rubber averaged 56 and 37% respectively (fig. 1).

Mean length of cuff, thickness, residual volume and the diameter of the cuff at residual volume are presented in tables III and IV.

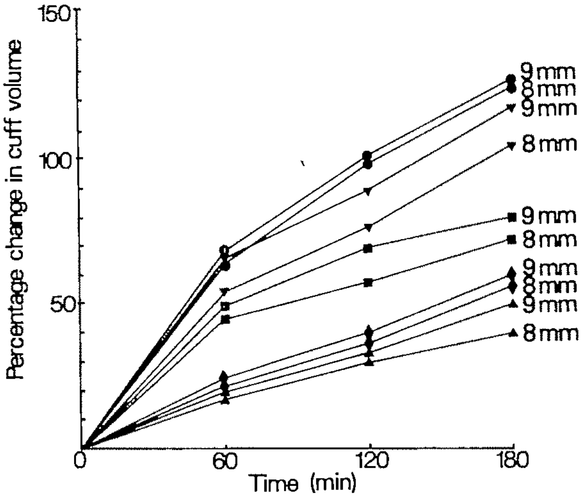

FIG. 1. Percentage change in cuff gas volume. ● = Mallinckrodt hi-lo; ▼ = Searle Sensiv; ■ = Portex Profile; ◆ = Leyland Cuftrac latex; ▲ = Magill red rubber.

DISCUSSION

The usefulness of cuffed tracheal tubes during artificial ventilation and their role in the prevention of aspiration have been well established in Europe. However, several complications relating to the cuffs have been reported. These include minor complications like sore throat, glottic and sub-glottic oedema and more severe complications such as mucosal erosion, cartilage nercrosis and eventual tracheal stenosis (Nordin, 1977; Lewis, Schlobohm and Thomas, 1978). The frequency of these complications is related to the design of the

TABLE II. *Effects of nitrous oxide–oxygen (70–30%) on the gas volumes (mean ± SD) in the cuffs of high-pressure tracheal tubes filled initially with 10 ml of air*

Tracheal tube	Size	Increase in cuff volume (ml)		
		1 h	2 h	3 h
Magill red rubber	8 mm	1.90±0.28	3.1±0.74	3.75±0.64
	9 mm	2.02±0.57	3.5±0.94	4.70±1.05
Leyland Cuftrac latex	8 mm	2.20±0.34	3.6±0.40	5.60±0.40
	9 mm	2.50±0.25	3.8±0.58	6.00±1.40

TABLE III. *Physical characteristics of cuffs of 8-mm tubes (mean ± SD)*

Tracheal tube	Length (mm)	Thickness (mm)	Residual volume (ml)	Diameter (mm)
Magill red rubber	41.0±0.5	0.375±0.025	0.0	12.0±0.25
Leyland Cuftrac latex	30.0±0.2	0.375±0.025	0.0	12.0±0.25
Portex Profile	38.0±0.44	0.125±0.025	11.5±0.25	27.0±0.35
Searle Sensiv	39.5±0.50	0.125±0.025	6.0±0.20	20.0±0.25
Mallinckrodt hi-lo	45.0±1.00	0.045±0.003	22.0±0.50	31.0±0.25

TABLE IV. *Physical characteristics of cuffs of 9-mm tubes (mean ± SD)*

Tracheal tube	Length (mm)	Thickness (mm)	Residual volume (ml)	Diameter (mm)
Magill red rubber	41.0±0.50	0.375±0.025	0.0	14.00±0.25
Leyland Cuftrac latex	30.0±0.20	0.375±0.025	0.0	14.00±0.25
Portex Profile	38.4±0.44	0.125±0.025	13.05±0.35	29.80±0.30
Searle Sensiv	39.5±0.50	0.125±0.025	6.90±0.20	22.25±0.25
Mallinckrodt hi-lo	45.0±1.00	0.045±0.003	26.00±0.50	32.00±0.25

cuff, the duration of the pressure exerted on the tracheal mucosa and the area of contact between cuff and tracheal wall. This study demonstrates that nitrous oxide and oxygen can permeate into the cuffs of tracheal tubes and increase the volume of the cuffs in both high-pressure and low-pressure air-filled cuffs. These findings suggest that overexpansion of the cuff during anaesthesia can lead to an increase in cuff pressure on the tracheal mucosa and it may be a significant cause of those complications related to cuffs.

Many factors govern the rates at which gases pass through organic films. The volume of gas (V) that will pass through the film is directly proportional to the difference in the pressure exerted by the gas on each face of the film ($p_1 - p_2$), the area of the film exposed (A) and the time (t) for which permeation occurs and is inversely proportional to thickness (X). This relationship may be expressed as:

$$V = \frac{P \times At(p_1 - p_2)}{X}$$

where P has a constant value for a specific combination of gas and cuff material at a given temperature and is known as the permeability constant or coefficient. Since permeability is dependent on both diffusion and solubility characteristics it is possible to write:

$$P = DS$$

where P, D and S are the permeability, diffusion and solubility coefficients respectively for a given permeant/cuff system (Brydson, 1966). Gas solubility obeys Henry's Law and is proportional to the partial pressure, whereas the rate of diffusion of gases through the membrane is proportional to their concentration gradient and inversely proportional to the square root of their molecular weight.

The nature of both permeant and cuff material influence permeability. The size, shape and molecular weight of a permeant affect the rate of diffusion, whereas polarity of the molecules has a pronounced effect on the solubility coefficient (Hennessy, Mead and Stening, 1967). The rate of diffusion through polymers used in the manufacture of cuff material depends on the size of gaps between their molecules, which in turn is determined by the physical state of the polymer. In rubber the molecular segments have considerable mobility, so the rate of diffusion is greater than in any other type of polymer. Permeability characteristics of a polymer are associated with variations in molecular weight, the chain length of the molecules, the presence of a double bond, the degree of polymerization, the nature and quality of plasticizer and inert filler content. In the case of polyvinyl chloride film, permeability is also influenced by temperature.

The maximum increase in the volume of the cuff occurred in Mallinckrodt hi-lo tubes (table I).

These cuffs had the largest length and diameter and therefore the largest surface area and minimum wall thickness. Although the cuffs of Portex Profile and Searle Sensiv tubes were of similar length and wall thickness, their residual volumes were different. The cuffs of the Searle Sensiv tubes had a small residual volume (6–6.9 ml) and when filled with 10 ml of air were stretched more, thus affecting their wall thickness and leading to a greater increase in the volume of the cuff.

The smallest increases in gas volume occurred in Magill red rubber and Leyland Cuftrac latex tubes probably as a result of their thicker wall, which presented a greater barrier to the diffusion of nitrous oxide and oxygen. However, if the inflated cuffs in this study were exposed to the nitrous oxide–oxygen mixture for long enough they would eventually contain gas at the same pressure and with the same composition as the gas mixture outside. The changes in the rate of change of cuff volume with time reflect a phase in this equilibrium process.

Stanley, Kawamura and Graves (1974) demonstrated that the diffusion of nitrous oxide caused a significant increase in gas volume in cuffs. Oxygen is less diffusable through the walls of cuffs and its contribution to the final volume in the cuff is considerably less. The diffusion of nitrogen out of the cuff was small despite its smaller molecular weight and the favourable concentration gradient (80% inside the cuff *v.* 0 outside). However, the factors governing the differences in partial pressure of the gases between the outside and inside of a cuff are complex. The pressure difference for each gas will be influenced by transfer of that gas into the closed space, by the transfer of other gases, and by any changes in pressure in the cuff consequent upon the changes in volume.

Stanley (1975) studied the effects of nitrous oxide on the volume and pressure of endotracheal tube cuffs in patients and found that the changes in volume were less *in vivo* than *in vitro*. One reason for this is that only the distal portion of the cuff, that is, the portion not in contact with the tracheal wall, is exposed to the inspired gases in patients, while the upper end of the cuff is exposed to atmospheric air. This will allow nitrous oxide to permeate the cuff from the lower end and progressively permeate to atmosphere through the upper end.

All cuffs are permeable to nitrous oxide, leading to increases in volume and pressure. The latter may be associated with an increased frequency of tracheal trauma. This may be overcome by inflating the cuff with a sample of the inspired mixture of gases rather than room air, or by monitoring the pressure in the cuff with a device attached to the inflation line. Variations of pressure within the cuff can be observed and corrected as necessary. Another alternative is to use a pressure relief valve which will bleed off excess gases but maintain the volume of the cuff and the pressure required to produce a tracheal seal.

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EFFETS DU PROTOXYDE D'AZOTE ET DE L'OXYGENE SUR LES VOLUMES DE GAZ DES MANCHONS DE TUBE TRACHEAL

RESUME

On a fait une étude sur les variations qui se sont produites dans le volume des manchons de 200 tubes trachéaux gonflés à l'air lorsqu'on les a exposés à 70% de protoxyde d'azote et à 30% d'oxygène. Nous avons mesuré la longueur, le diamètre et l'épaisseur de paroi de chaque manchon de même que son volume résiduel. Des augmentations dans le volume de gaz ont

été constatées dans tous les tubes, en fonction du temps. Les tubes trachéaux ayant des manchons à basse pression ont été plus perméables au protoxyde d'azote et à l'oxygène que les tubes dotés de manchons à haute pression. Les implications de cette découverte et les facteurs qui gouvernent le taux de transmission des gaz à travers le matériau du manchon sont débattus dans cet article.

AUSWIRKUNGEN VON STICKOXYDUL UND SAUERSTOFF AUF TRACHEALSCHLAUCHMANSCHETTEN-GASVOLUMEN

ZUSAMMENFASSUNG

Es wurden die Änderungen beim Volumen der Manschetten von 200 mit Luft aufgeblasenen Trachealschläuchen während des Aussetzens an 70% Stickoxydul und 30% Sauerstoff studiert. Die Länge der Manschette, ihr Durchmesser, Wandstärke und Restvolumen wurden alle gemessen. Eine Zunahme des Gasvolumens trat bei allen Schläuchen in Abhängigkeit von der Zeit ein. Die Trachealschläuche mit den Niederdruck-Manschetten waren Stickoxydul und Sauerstoff gegenüber viel durchlässiger als Trachealschäuche mit Hochdruck-Manschetten. Die Folgerungen aus diesem Befund und die Faktoren, die die Durchgangsgeschwindigkeiten der Gase durch Manschettenmaterial bestimmen, werden diskutiert.

EFECTOS DEL OXIDO NITROSO Y DEL OXIGENO EN LOS VOLUMENES DE GAS DE LOS ANILLOS DEL TUBO TRAQUEAL

SUMARIO

Se estudiaron los cambios del volumen de los anillos de 200 tubos traqueales inflados con aire, bajo la exposición a una mezcla de 70% de óxide nitroso y de 30% de oxigeno. Se midieron la longitud del anillo, su diámetro, el grosor de la pared y el volumen residual. Tuvieron lugar incrementos en el volumen del gas en todos los tubos, siendo estos incrementos función del tiempo. Los tubos traqueales con anillos de baja presión fueron más permeables al óxido nitroso y al oxigeno que aquellos de alta presión. Se discuten las repercusiones de estos resultados así como los factores que regulan los regímenes de transmisión de gases a través del material del anillo.

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CORRESPONDENCE

ATROPINE PREMEDICATION AND RESPIRATORY COMPLICATIONS

Sir,—Jones and Drummond (1981) have shown that premedication with atropine does not influence the frequency of postoperative respiratory complications. However, they do not make a recommendation for routine use, or otherwise, of atropine in premedication. Studies on the effects of atropine administration on ciliary activity have shown conflicting results. Experimental studies in dogs have not shown any inhibition of mucociliary transport (Chopra, 1978; King, Cohen and Viires, 1979), but in anaesthetized patients, atropine has been shown to decrease it (Annis, Landa and Lichtiger, 1976).

One could deduce from the report of Jones and Drummond (1981) that atropine was not helpful in the reduction of chest complications after operation. In a survey of anaesthetists (Mirakhur et al., 1978) it was found that one-third of anaesthetists did not use anticholinergic drugs routinely in premedication. A principal reason was that they felt that atropine made the secretions viscid and perhaps difficult to expectorate. The omission of routine administration of anticholinergic premedication does not seem to influence the course of anaesthesia in any adverse manner (Kessell, 1974; Leighton and Sanders, 1976; Mirakhur and Dundee, 1979; Mirakhur, Dundee and Connolly, 1979).

If atropine does not prevent respiratory complications, why use it routinely in premedication in view of the discomfort of a dry mouth and the pain of an i.m. injection?

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INTENSIVE CARE UNIT REVISITED

Sir,—The reaction to being a patient in an Intensive Care Unit is the subject of much discussion and speculation amongst medical and nursing staff. Having spent some considerable time working in I.C.U.'s, both as a registrar in anaesthesia, and in nephrology, I had gathered my own vicarious impressions. The opportunity to gain personal insight resulted from a car accident in which I sustained a number of injuries including a fractured maxilla and facial trauma, despite the protection of a seat belt.

Following assessment in the Accident department I was transferred to a surgical ward, and from there, in anticipation of airway problems, to the I.C.U. The information that I was to be transferred was discussed with me by a number of people, who adopted two distinctly different approaches. The first was the comment that my transfer was a measured response to a recognized problem, and that I could be managed more safely in the I.C.U. Since I was aware of partial airway obstruction, as I believe any tolerably intelligent person would have been, this approach was appropriate. The second, and perhaps understandable, approach was one of apology. I am sure that I have adopted this sympathetic attitude in such circumstances, but the effect is to imply that transfer to an I.C.U. reflects grave deterioration, and is not uncommonly a pre-mortem event. I am certain that the positive approach is better.

I know many of the I.C.U. staff, and I suppose that this was potentially a cause of embarrassment. However, there was a calm acceptance by the nursing staff that I could not care for myself and needed help. I was equally content to be the patient, and the change of relationship was effected without difficulty. Similarly, the medical staff were frank in discussing the anaesthetic risks of surgical reduction and fixation, and were clear about the possible need for a tracheotomy. I was more reassured by their clarity than I would have been by bland reassurance, and again I am sure that this would be the reaction of any patient who was aware of his precarious state.

To my relief tracheotomy was avoided, but the night after operation was frightening when my nasopharyngeal tube became dislodged and I had to breathe through wired teeth and swollen lips. I was terrified, and, interestingly, was much more reassured by the presence of a nurse than I was by the use of monitoring equipment. When the nurse left me to care for another patient I began to panic, and when she returned I was calmed. One can speculate as to whether an understanding of monitoring equipment provides more or less reassurance. However, I am left in no doubt that, whilst monitoring devices may well be essential, a strong nursing presence is of more benefit to frightened patients.

What, then, are my lasting impressions? Nothing startlingly original; only confirmation that clarity of explanation and constant reassurance are essential components of intensive care management. Those who seek to reduce patient–staffing ratios should temper their decisions with humanity.

Hugo Mascie-Taylor
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DETECTION OF WAKEFULNESS DURING GENERAL ANAESTHESIA

Sir,—A preliminary report (Breckenridge and Aitkenhead, 1981) suggests that the isolated forearm technique (Tunstall, 1977) is impractical and less sensitive than standard clinical signs for the detection of light planes of general anaesthesia when muscle relaxants are used. I hold a contrary opinion after almost 2 years' experience of the technique, and since this may be related to differences in detail I shall describe my method fully.

One arm is used for the indwelling cannula and for measurement of arterial pressure; the other arm is free. An ordinary sphygmomanometer cuff is wrapped around this arm over the patient's gown or some padding (to prevent bruising). Just before induction of anaesthesia, the patient is asked to "squeeze my hand" and then "relax your fingers". This is repeated to ensure that the patient can comply with the instructions and the patient is told "if ever you feel uncomfortable you can squeeze my hand". No other explanation is given. During induction the arm is partially exsanguinated by being held vertically and when the patient is asleep the cuff is inflated to a pressure of 250 mm Hg and clamped. The arm is lowered and the neuromuscular blocking drug is injected through the cannula in the other arm. The patient is instructed to "squeeze my hand" from time to time, especially just before and after tracheal intubation and incision. The cuff is deflated after 15–20 min, by which time the circulating concentration of neuromuscular blocking drug is too small to produce neuromuscular blockade (this can be verified with a nerve stimulator). If the isolating cuff is placed proximally on the arm the elbow can be bent and the arm retained in the patient's gown or, alternatively, the arm can be strapped to a board so that movements do not interfere with the surgery.

Three types of response may be seen:

(1) The hand moves quite clearly according to command, both squeezing and relaxing as requested. Questions can be phrased to discover if the patient is in distress (Wilson, 1980) or willing to remain awake throughout the operation (Tunstall, 1980).

(2) The movements occur in response to the stimulus of intubation or surgery and are not related to commands.

(3) Responses to command, intubation or surgery are absent.

If the patient can respond to questions using the isolated forearm and indicates distress, I give an increment of thiopentone or add 0.5% halothane to the inspired gas mixture even though there may be no subsequent memories of the operation. Arguments that have been given for doing this are:

(a) It is morally unacceptable to allow a patient to remain in pain or distress even if there is no memory of the suffering.

(b) The amnesic aspect of wakefulness cannot be guaranteed and it is probable that a wakeful patient is more likely than a non-wakeful one to complain later of unpleasant recall.

(c) A wakeful patient may sustain adverse effects as a result of inadequate anaesthesia even if there is amnesia.

Movements of the second type are perhaps reflex, but as a conscious person can behave reflexly, I give anaesthetic supplements if the movements persist. Absence of response suggests that the patient is adequately anaesthetized and there will be no subsequent factual recall. However, a large study would be required to establish this point.

Since my previous report (Wilson, 1980) I have seen several patients, anaesthetized by myself or by colleagues, express distress detected by isolated forearm technique. Breckenridge and Aitkenhead (1981) may have failed to obtain responses to commands because the instructions were presented too infrequently and consequently they did not coincide with the critical periods of tracheal intubation and of incision.

Clinical signs of anaesthesia cannot be relied upon to detect awareness (Hutchinson, 1960; Parkhouse, 1960; Bahl and Wadwa, 1968; Robson, 1969; Barr and Wong, 1973; Abouleish and Taylor, 1976; Silbergleit, 1976; Barr et al., 1977) and expensive methods of recording electrical activity of the brain have not yet been of proven value. The obvious alternative is to *ask* the patient if he is awake. This can be done simply and cheaply using the isolated forearm technique and I encourage readers to give it a fair trial to ensure that the anaesthesia they provide is as adequate as they would like to believe.

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KNOWLEDGE ON THE CHEAP

Sir,—The dissemination of medical information is achieved in three ways. A scientist with something to add to the sum total of knowledge may submit an article to the editor of a scientific journal. The editor usually consults with one or more experts in the subject, and if the content is deemed worthy of publication, the article is published. No payment is made by the journal to the contributor and none is expected; to have contributed to knowledge is reward enough.

If the first editor approached does not regard the contribution as worthy of publication the scientist may hawk the article round a series of editors until one is found who will accept it. It is even possible, in some disciplines, to find a journal which will publish what is offered to it at the author's expense. So great is the pressure on scientists in some countries to have visible evidence of work done that a journal of that type manages to survive in spite of the disapproval of the more orthodox scientific community.

Another type of publication is exemplified by the postgraduate educational issues of *British Journal of Anaesthesia* and in a different way by the unsigned editorial columns of the great medical weeklies in the U.K. Those who provide the material for such journals count it an honour to be asked to contribute. Signed articles are written for such journals at the invitation of the Editor. All the world can see, not only from the quality of the article but from the fact that an Editor has picked a worker in a particular field as a contributor, that the man so chosen deserves to be highly regarded by his fellows. In the case of the U.K. weeklies, nearly the same situation exists, for it is an open secret that certain of our colleagues provide regular annotations for those journals. Further, those who contribute to the columns of such publications have also the satisfaction of knowing that they are able to guide the thinking of colleagues and indeed to be leaders of their profession, whatever the pecuniary rewards.

Those who write text books and, perhaps even more, chapters in text books are exploited. To be acceptable to a publisher of a medical text book an author must be established as an authority. Yet the standard reward for writing anything but the most successful text book (10% of the sales revenue for the first 1000 copies and 12½% thereafter) will never repay the author for the hours upon hours of time spent in the preparation of his book. Indeed, if he has to bear it himself it will barely repay the cost of typing the manuscript. The reward offered to the author of a chapter in a multi-author book is derisory—an anaesthetist could earn more in one hour of clinical private practice.

The author of a textbook can perhaps sublimate his frustration in the belief that his book contains something which is of unique value to his reader and thereby persuade himself that the hourly rate of 10p or so which he receives for his work is unimportant. If he is a whole-time member of a University Department he may have been able to find much of the time required for the preparation of the book within ordinary working time. Universities seem to approve the writing of books by their staff members, although not enough notice has been taken of the tremendous subsidy they afford for medical publication. Not only do they help the authors themselves; departments of medical illustration help greatly in the provision of figures and illustrations. Departmental secretarial help, too, is also available for University-based authors.

The non-university clinician who sets out to write a book or chapter quickly finds that his task makes enormous inroads to his free time and on his pocket. A few enthusiasts will still feel that to have written a book and set down their views for their colleagues is of itself a sufficient return; others who are capable of making very worthwhile contributions to knowledge become discouraged and give up, leaving the literature poorer.

To some extent the rewards of sole authors have increased *pari passu* with the increase in the price of books. The rewards offered to those who are asked to provide chapters for multi-author books, to be paid for on a cash basis, have scarcely altered over the past few years. Our medical publishers should review the position with a view to encouraging those who could make a worthwhile contribution, but are discouraged from doing so.

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POTENTIAL HAZARDS OF ANTISTATIC HOSE

Sir,—I read with interest the letter from Tilling and Hancox (1981). I have long thought that anti-static precautions in operating theatres were a waste of money, and now we have evidence that they may be dangerous.

In effect it was demonstrated that anti-static breathing hose may become more electrically conductive than is safe, and capable of carrying a dangerous leakage current. The consequence of this is that we must test their conductivity regularly and discard those (otherwise sound) that fail the test if we are to protect our patients properly.

In this hospital it is about 17 years since either ether or cyclopropane were used. All the surgeons use diathermy, and would resist any suggestion that they should operate without it. We have acquired apparatus that carries a warning against use in the presence of inflammable agents, without being worried.

When one considers the extra purchase price of anti-static rubber goods, and the need for electrical testing, and occasional premature replacement of these goods, the few anaesthetics administered with ether or cyclopropane must be unbelievably expensive in money and in the time of skilled staff.

Surely we could spend this on something more likely to benefit patients?

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HYPOTENSION AFTER INTERCOSTAL NERVE BLOCK

Sir,—The article entitled "Hypotension after intercostal nerve block during thoracotomy under general anaesthesia" raises a significant point (Skretting, 1981). Similar reports and reports of total spinal block following intrathoracic block of the intercostal nerves have been published (Benumof and Semenza, 1975; Cortell et al., 1978; Moore and Reitan, 1978). The common factor in these reports was the surgeon attempting to block the intercostal nerves under direct vision. We have performed unilateral and bilateral percutaneous blocks of the intercostal nerves in more than 12 000 patients for thoracic and upper abdominal surgery and for diagnosis and therapy. Profound hypotension with or without total spinal anaesthesia has yet to occur.

On the basis of other reports (Atkinson, Rushman and Lee, 1977; Nunn and Slavin, 1980), Skretting theorizes that the local anaesthetic solution can spread centrally to the paravertebral space of the intercostal nerve injected and into the extradural space, thus effecting a sympathetic blockade which is responsible for the reported hypotension. In a previous study using computer tomography, we showed that, when percutaneous injection of an intercostal nerve is made in the groove of the rib at its angle, the solution does not spread into the extradural space (Moore, Bush and Scurlock, 1980). Nor did hypotension result.

Using Nunn and Slavin's article (1980) as a basis, Dr Skretting further theorizes that, in addition to the nerves of the rib injected, the intercostal nerves of the ribs above and below the injected rib are also anaesthetized. Our investigations showed, however, that the injection of solution into the groove of one rib blocks only that groove's intercostal nerve, and not the ones above and below (Moore, Bush and Scurlock, 1980; Moore, 1981).

When the intercostal nerve is injected under direct vision, an attempt is usually made to inject it intraneurally. With the percutaneous approach, this is not done. In fact, the anaesthetist tries to avoid intraneural injection by jiggling the needle in the groove of the rib, that is, moving it forward and backward approximately 2–3 mm as the local anaesthetic solution is injected. If the surgeon performs an intraneural injection proximal to the angle of the rib or close to the point where the rib articulates with the vertebra, the solution can spread centrally in the perineural spaces of the nerve or in a long dural cuff, resulting in total or partial spinal anaesthesia (Moore et al., 1954; Benumof and Semenza, 1975).

Percutaneous block of the intercostal nerve(s) is a much safer technique than injection under direct vision. To date, percutaneous block has avoided hypotension and total spinal anaesthesia, both of which have been reported from direct injection of the intercostal nerves during thoracotomy. Perhaps the surgeons should consider the alternative intrathoracic method of blocking the intercostal nerve for pain relief after operation—namely, freezing (Nelson et al., 1974). Finally, if the intercostal nerves are injected with a local anaesthetic drug intraneurally under direct vision, hypotension with or without spinal block should be an expected complication.

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Skretting, P. (1981). Hypotension after intercostal nerve block during thoracotomy under general anaesthesia. *Br. J. Anaesth.*, **53**, 527.

Sir—We observed that intrathoracic intercostal nerve block under general anaesthesia resulted in hypotension and a decrease in heart rate in five of 30 blocks performed. We attributed this to paravertebral spread of the local anaesthetic drug affecting sympathetic nerve fibres. None of our patients showed signs of total or partial spinal anaesthesia.

In an attempt to explain the hypotension and the associated moderate decrease in heart rate I theorized, on the basis of other reports (Atkinson, Rushman and Lee, 1977; Nunn and Slavin, 1980), that the local anaesthesia solution may have spread to the paravertebral space of the nerve injected and into the extradural space, thus effecting sympathetic blockade. According to Nunn and Slavin, spread of the anaesthetic round the internal aspect of the rib and into the spaces above and below may also occur.

I had noted the recent studies of Moore, Bush and Scurlock (1980) showing that the solution does not spread into the extradural space, and of Moore (1981) showing that injecting solution into the groove at one rib blocks only that intercostal nerve. These results are contrary to the previous reports.

The observed hypotension and the associated decrease in heart rate was, in my view, attributable to a sympathetic block of thoracic nerve fibres. The period of time between the decrease in arterial pressure and the administration of the drug (mean 11.6 min), the effectiveness of ephedrine and the absence of any sign of spinal anaesthesia may support this theory.

I do not think intercostal nerve block *per se* causes hypotension. However, one important point in my conclusion was the circumstances under which the block was performed: namely general anaesthesia and open chest. According to Guyton (1977) both general anaesthesia and thoracotomy increase considerably sympathetic activity. An unintentional sympathetic block will more or less eliminate this defence reaction.

Our surgeons did not perform intraneural injection, but tried to deposit the anaesthetic solution round the intercostal nerve.

I agree with Moore's conclusion that percutaneous block normally does not cause hypotension, and our experience is that this approach is a good and safe method under other circumstances. During thoracotomy the block may be performed better after closure of the chest or after operation. It would have been interesting to perform percutaneous intercostal nerve block during thoracotomy under general anaesthesia before closing the chest for comparison.

Per Skretting
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Sir,—The report by Skretting (1981) of the appearance of hypotension occurring shortly (3–20 min) after intercostal nerve block under general anaesthesia for thoracotomy could be a result of the intraneural injection of the local anaesthetic drug. The longitudinal spread of intraneurally (intrafascicular or extrafascicular) injected substances has been well documented (French, Strain and Jones, 1948; Brierley and Field, 1949; Moore et al., 1954; Selander and Sjostrand, 1978). The relatively small mass of local anaesthetic reaching the subarachnoid space via this route might be sufficient to effect a differential spinal anaesthesia (Sarnoff and Arrowhead, 1946; Winnie and Collins, 1968) affecting primarily the preganglionic sympathetic fibres resulting in hypotension and bradycardia.

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EXTRADURAL FENTANYL AND POSTOPERATIVE ILEUS IN CATS

Sir,—In recent years extradural administration of opiates has become widely used in the treatment of pain. Apparently, opiate action entails a selective blockade of pain pathways, without obvious alterations in tactile perception, somatomotor control or arterial pressure (Dirksen and Nijhuis, 1980). On the other hand, painful stimuli are potent activators of the spinal sympathetic outflow, reflexes which sometimes are organized at the propriospinal level. An example of the latter is the gastrointestino–gastrointestinal (GI–GI) reflex which can be elicited by painful intra-abdominal stimuli or distension within the gastrointestinal tract, leading to inhibition of gastrointestinal motility. This reflex is clearly involved in postoperative ileus (Furness and Costa, 1974). We were interested to determine if the GI-GI reflex is altered by extradural injections of fentanyl.

Cats were anaesthetized with chloralose and the lungs ventilated artificially. The vagi in the neck were cut and arranged for efferent stimulation. Systemic arterial pressure, heart rate and gastric volume were recorded, the latter with a transoesophageal balloon. Following midline laparotomy, a jejunal segment was tied at the ends and cannulated. An extradural catheter was inserted through a small lumbar laminectomy, with its tip in the mid-thoracic region.

The vagi were stimulated in the neck to increase gastric tone. This vagally-induced tone was promptly reduced by distension of the isolated intestinal segment, indicating activation of the GI–GI reflex. Distending pressures of 20–150 cm H_2O were used to induce graded and reproducible responses. Fentanyl 0.01–0.05 mg given extradurally abolished or substantially reduced the inhibitory reflex with a latency of 5 min or less (fig. 1). This effect could be reversed rapidly by naloxone 0.04–0.1 mg given either i.v. or extradurally. These doses of fentanyl had no effect on the GI–GI reflex when given i.v.

Thus, fentanyl given extradurally, but not systemically, inhibited the GI–GI reflex by an opiate-specific action. The mechanism may have been a depression of transmission of

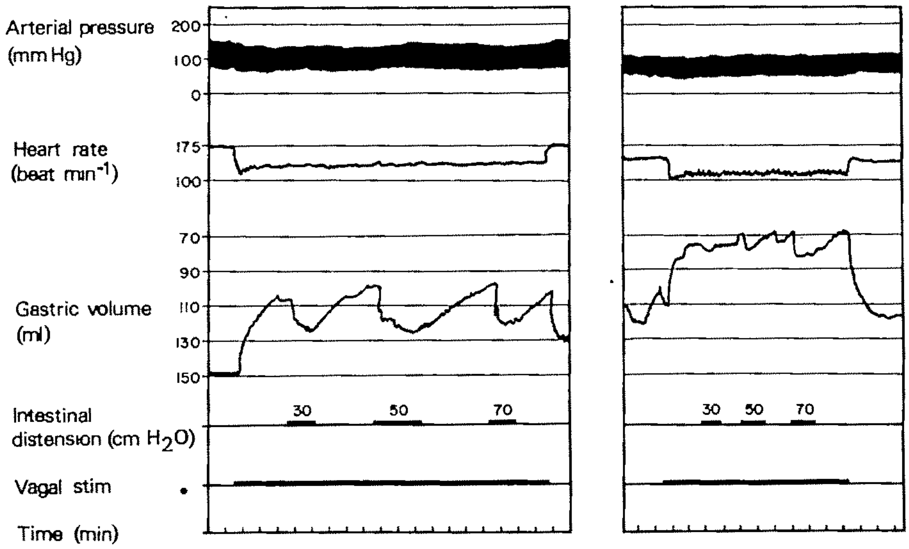

FIG. 1. Cat 3.1 kg. The effect of intestinal distension before and after (second panel) extradural fentanyl 0.05 mg.

sensory information in the spinal cord (Kitahata and Collins, 1981), requiring high local concentrations of the drug. A recent editorial in this journal (Hall, 1980) noted that very high doses of fentanyl given i.v. can prevent several of the hormonal and metabolic changes during surgery. The present observations point to the possibility that at least part of this action may be a result of spinal mechanisms; the elucidation of this problem requires further study.

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HYPERBARIC NITROUS OXIDE AND MALIGNANT HYPERPYREXIA

Sir,—Nitrous oxide has been suggested as a weak trigger in malignant hyperpyrexia (MH) (Ellis, Clarke and Appleyard, 1974), implying that the use of greater concentrations of nitrous oxide might lead to MH episodes in susceptible patients. If true, this might explain episodes of MH that occurred in a patient who was anaesthetized with barbiturates, opiates and nitrous oxide (Fitzgibbons, 1981).

We examined the triggering action of nitrous oxide in a cylindrical hyperbaric chamber (90 cm long and 44 cm diameter) in six Poland China swine 20–40 kg in weight. Three pigs were susceptible to MH (halothane challenge), two were not (halothane–suxamethonium challenge) and one was "in-between": Pa_{CO_2} increased to 8.7 kPa and BE decreased to −12 after halothane and suxamethonium; however these changes occurred slowly and then gradually reverted to normal without therapy (Gronert, 1979). MAC for nitrous oxide in swine is likely to be between 133 and 213 kPa (Quasha, Eger and Tinker, 1980).

The pigs received atropine 0.4 mg i.v. and were anaesthetized with thiopentone 15–20 mg kg^{-1}; the trachea was intubated and the animals breathed 70% nitrous oxide in oxygen while an arterial cannular was inserted. The pig and the transducer were put into the chamber and depth of anaesthesia was monitored visually by the pattern and frequency of spontaneous ventilation. Ventilation became slower and more regular as anaesthesia deepened; eventually ventilation became uneven and jerky, but Pa_{CO_2} remained less than 7.6 kPa even to the point of apnoea. Oesophageal temperature was monitored by thermistor. Arterial pressure, heart rate, and blood-gas tensions were monitored via the arterial catheter; samples were withdrawn via a stopcock in the wall of the chamber. A 12-litre flow of nitrous oxide and oxygen was sufficient to prevent carbon dioxide accumulation within the chamber, and gas flows were adjusted to maintain chamber Po_2 (Beckman paramagnetic oxygen analyser) at 27–73 kPa with arterial Po_2 ranging from 11.2 to 44 kPa.

All pigs responded similarly to hyperbaric nitrous oxide. Arterial pressure and heart rate were stable, and temperature decreased slowly. Exposure times are shown in table I.

TABLE I. *Exposure time (min) to hyperbaric nitrous oxide*

	Chamber pressure (kPa)			
	147–159	160–172	173–187	Total
MH pigs (3)	5	15	75	95
	10	70	—	80
	62	—	—	62
Normal pigs (2)	13	45	15	73
	8	47	—	55
In-between pig (1)	23	63	—	86

No episodes of MH occurred, as shown by normal values for Pa_{CO_2}, base excess, muscle tone, and temperature. Two MH pigs and one normal pig became apnoeic in the chamber, at respectively P_{N_2O} 193, 165, and 90 kPa (the last episode occurred during decompression). Apnoea was treated by decompression within 3–4 min and immediate hyperventilation after the pig was removed from the chamber. One of the apnoeic pigs (90 kPa) died, with signs of decompression sickness, "the bends."

We presume that these exposures were of sufficient length and depth to exclude anaesthetic concentrations of nitrous oxide as a trigger in porcine MH.

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Rochester, U.S.A.

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BOOK REVIEWS

Clinics in Obstetrics and Gynaecology. Volume 7, no. 3. Operative Obstetrics. Edited by Ian MacGillivray. Published by W. B. Saunders, London. Pp. 700; illustrated; indexed. Price £9.75.

This is one of the now well-established and respected series of up-to-date reviews of obstetric and gynaecological topics. Few anaesthetists would dispute that operative techniques cannot be learned from books alone and that the art and craft of surgery is learned by practical experience. This view is shared by the editor, whose aim has been an objective consideration of the indications for the various obstetric procedures and an assessment of their complications. Established techniques such as forceps delivery and Caesarean section are considered along with newer manoeuvres such as fetoscopy, amnioscopy and amniocentesis. Simple procedures may be the most controversial: witness the widely divergent views on the surgical induction of labour in many centres on both sides of the Irish Sea. Traditional operations such as the vaginal delivery of the infant presenting by the breech are being abandoned by many obstetricians in favour of delivery by Caesarean section. While such policies can be jusified in the fetal interest, what of the risks to the mother? Not the least of these risks is the risk of general anaesthesia. The obstetrician who writes on breech delivery prefers to have an anesthetist standing by to administer general anaesthesia to supplement pudendal nerve block. This somewhat old-fashioned policy is needlessly dangerous for the mother and deprives mother and infant of the benefits of a controlled delivery under extradural analgesia. The hazards of forceps delivery under general anaesthesia are acknowledged and it is emphasized that almost all forceps delivery can and should be performed under regional analgesia.

The chapter by M. E. Tunstall on Anaesthesia for Obstetric Operations is of special interest to anaesthetists. Written for obstetricians, it is concerned largely with anaesthetic causes of maternal mortality and the problem of awareness during general anaesthesia for Caesarean section. These are topics on which Tunstall is an authority and the chapter may be seen as a declaration of faith by its author. In many respects it is a masterly combination of the scholarly and the practical, although the chapter is unbalanced in its near-neglect of regional techniques. The views expressed on topics such as failed intubation and the role of alkalis in the prevention of Mendelson's syndrome command respect and are carefully reasoned. They are supported by references as recent as 1980 and this is a matter for congratulation of author, editor and publisher. Some points of detail cannot go unchallenged. Can the head-down, left lateral position for the induction of anaesthesia really provide the complete answer to the prevention of deaths as a result of aspiration? As Tunstall states, this position makes intubation difficult and difficult or failed intubation is now emerging as an important cause of death under anaesthesia. Also controversial is the advocacy of awake intubation under topical anaesthesia when difficult intubation is anticipated, the stomach is full or the patient is severely collapsed and bleeding. There is a closely reasoned discussion on the merits and demerits of alkali therapy, cimetidine, metoclopramide and glycopyrrolate. Perhaps the answer to many of the problems is the substitution of extradural or subarachnoid anaesthesia.

On the subject of awareness, Tunstall gives a clear and balanced account in which he emphasizes the narrowness of the gap between fetal depression and maternal awareness. The isolated forearm technique, although ingenious and valuable, is perhaps not generally utilized and may be too "fussy" for the busy, single-handed anaesthetist who is advised to use a 50 : 50 nitrous oxide and oxygen mixture supplemented by 0.5% halothane. Interesting animal experimental evidence which suggests that volatile agents in concentrations of up to 1.5 MAC may improve utero-placental blood flow, lessen fetal acidosis and presumably substantially reduce the frequency of awareness are not mentioned, perhaps because such techniques might cause unacceptable relaxation of the myometrium.

The admirable obstetrician who wishes to attain an adequate knowledge, for his purposes, of the problems of obstetric anaesthesia may find some of the detail in Tunstall's chapter surplus to his requirements. The basic principles set out should be assimilated by every obstetrician who ever requests a general anaesthetic for a pregnant woman. This, in most respects, well-informed and up-to-date book is good value at £9.75 for 700 pages and is likely to be read by many obstetricians. It is to be hoped that they will bear in mind the anaesthetic implications of all operative obstetrics and that they will always remain conscious of the responsibility of the obstetrician who requests or "insists upon" a general anaesthetic when regional analgesia would perhaps have been better and safer for mother and child. Anaesthetists, too, must accept the need to provide regional analgesia for obstetric patients and must endeavour to reduce the risks of general anaesthesia.

Donald D. Moir

Progress in Respiration Research. Clinical Importance of Surfactant Defects, Vol. 15. Edited by P. von Wichert. Published by Karger, Basel, Munchen, Paris, London. Pp. 319; illustrated; indexed. Price $98.25.

The two main functions of pulmonary surfactant are to help prevent fluid from leaking into the alveoli from the interstitial space and to enhance the expansion of air-filled alveoli. These functions may be deficient in two clinical conditions, pulmonary oedema and the respiratory distress syndrome. This book is the proceedings of a Symposium held at the end of 1979, the intention of which was to discuss the clinical functions of the surfactant system. The 39 papers (two of which were not submitted for publication) represent the contribution of almost 100 research workers deracinated from their laboratories around the world. The papers are divided into four sections: Basic Problems, Experimental Findings, Respiratory Distress, and Therapeutical (*sic*) Approaches. A basic problem for me was the absence of any form of introductory review. Before immersing himself in this book the reader may obtain such a review by studying the editorial in *Thorax* (36, 1–4, 1981), entitled "What is the true role of surfactant in the lung?". This editorial questioned most of the accepted functions of surfactant other than its role as an alveolar stabilizing agent and would have formed an interesting introduction to the Symposium. However, armed with this controversial editorial, a more objective view may be obtained of much of the research published in this proceedings.

Under the heading "Basic Problems" is to be found: isolation of alveolar type II cells; surfactant synthesis; secretion and clearance; surface properties and the role of surfactant in transepithelial movement of fluid. In this section a paper on the Pulsating Bubble Technique goes "over the top" in its search for clinical relevance and probably has the Editors of the *Journal of Irreproducible Results* panting with excitement. An outline of the discussion is as follows: Chloroform or halothane vapour (concentration 35%!) had a dramatic effect on surface tension which was not found with acetone, ether or fluothane (*sic*)! This result explained the safety of ether compared with the potential lethal risk of cholorform and halothane! Anaesthetists will be comforted to know that the author reported that at concentrations less than 20% neither chloroform nor halothane vapour had any effect on surface tension!

A provocative paper on surface tension and pulmonary oedema aroused comment on the extraordinary low reflection coefficient for protein at the alveolar epithelial surface. This value was calculated for transport of protein from alveolus to interstitial space and may not be appropriate for protein transport in the clinically relevant direction.

This section is followed by Experimental Findings. This was concerned in part with the control of surfactant secretion and emphasized the important role of both sympathetic and parasympathetic pathways. Also considered were the effects on surfactant of inhaled dusts, amphiphilic and other drugs, oxygen and detergents. Much of this section was concerned with the rat, rabbit and dog, but of clinical interest was the comparison of L/S ratio, surface tension and coagulation assay to predict fetal lung maturity.

In the RDS section are to be found studies on the problems of surfactant maturation. An interesting idea was expressed that, under some circumstances, the surfactant may be so closely packed that it behaves as a solid, rather than as a liquid. This theory implies that surface tension will decrease to zero under these conditions. In discussion, however, it was pointed out that the degree of compression required to achieve this solidification occurs only if the chest is opened and the lungs collapsed. I was not too clear what clinical advances, if any, were being described in this section. Clinical relevance, which was alleged to be the principal focus of the symposium, was often not mentioned, or included as a vaguely worded postscript.

The final section was concerned with therapeutics. A number of drug actions on surfactant systems were described, namely Ambroxol, steroids, antioxidants and the use of supplementary surfactant. One of the most interesting observations was that administered surfactant may prevent the development of bronchiolar epithelial lesions during artificial ventilation. This could well be important in the problem of avoiding ruptured lung when ventilating patients with stiff lungs.

This Symposium contains a number of fascinating presentations which the clinical investigator will find of great interest. The main deficiency is the lack of introductory analysis of the problem and a concluding synthesis of the advances in knowledge made in the Symposium. The discussion section is often one of the most useful aspects of such a Symposium, highlighting aspects of the previous paper that are either controversial or just plain wrong. The discussion sections reported here seem to be heavily condensed versions of the actual proceedings, are rather flat, and are in sharp contrast to the marvellous reservoirs of anecdote found in the discussion section of the C**A symposia.

J. Gareth Jones

Neonatal Anaesthesia; *Current Topics in Anaesthesia, Series 5.*
By David J. Hatch and Edward Sumner. Published (1981) by Edward Arnold, London. Pp. 206; illustrated; indexed. Price £14.95.

Drs Feldman and Scurr have set out to fill a need in anaesthetic literature by acting as general editors of the *Current Topics in Anaesthesia* series. Their stated aim is to produce authoritative reviews, of a concise nature, which will meet the demands of continuing education in anaesthesia.

To write for this series is, therefore, a demanding task. This is especially the case when the standards set by the previous four issues have been high and because a new, up to date, authoritative view of neonatal anaesthesia is badly needed.

Drs Hatch and Sumner tackle this task by allocating the first 40 pages to a consideration of perinatal physiology. This seems to have become a traditional introduction when the subject of anaesthesia for children is presented and often seems to the reader to be a means of expanding a book. In this case it is a pleasure to find that this information is entirely relevant, well presented and a mine of information of value to the practising anaesthetist.

The preparation of a neonate for surgery is described in the following 18 pages. The distillation of this large subject into so small a space is a feat which does not allow of much discussion, but again enables the reader to find the important information which he may need.

The third section, perhaps the most important of all, is devoted to the basic principles of anaesthesia for the neonate and has been allocated 30 pages. Details of the armamentarium, the induction of anaesthesia, intubation, i.v. cannulation, relaxants and patient care during anaesthesia are well described.

The fourth chapter deals with anaesthesia for specific conditions and 58 pages deal with aspects of management which require special consideration. The range is wide, from the classic problems of management of babies with tracheo–oesophageal fistula to anaesthesia for neurosurgery and cardiac surgery. The advice given is practical and reflects the experience and practice of the authors.

The chapter on postoperative care deals with basic aspects and, the authors state, does not attempt to deal with the vast area of neonatal intensive care. This results in a section which is sparse by comparison with the others and yet contains a section on methods of measuring lung mechanics which will not be of practical value to the average neonatal anaesthetist.

The final pages deal with resuscitation of the newborn and valuable appendices on associated medical conditions, drug doses and normal physiological values.

There are in this book some aspects of a detailed nature with which any practising neonatal anaesthetist might disagree, but this reflects a variation in technique which must exist in an area where there is art as well as skill. The detail is sometimes important, however, and your reviewer would expect support for his contention that the use of atropine 0.2 mg for a neonate is excessive. Apart from these details and disappointment with the quality of reproduction of x-ray plates, the presentation is laudable.

This book exceeds the standard of its predecessors, it is eminently readable, it is extremely useful and its authors are to be congratulated. It should be read by all anaesthetists, especially examination candidates, and it ought to be owned by all those who have to manage anaesthesia for small children.

J. S. Inkster

Principles of Clinical Measurement. By M. K. Sykes, M. D. Vickers and C. J. Hull. Published by Blackwell Scientific Publications. Pp. 325; illustrated; indexed. Price £21.00.

This is the second edition of Sykes and Vickers' *Principles of Measurement for Anaesthetists*, which first appeared in 1970. In the preface to the new edition, referring to the recent improvement in the standard of measurement technology and growth in the extent of its clinical application, the authors state that the book is now aimed at a wider audience than was the first edition. This policy is reflected in the change of title and in the recruitment of a third author, whose main responsibility has been for the parts dealing with electronics. The book retains the same structure as the original, being divided into three parts (General Principles and Instruments; Specific Measurements; Statistics) and most of the material from the first edition has been retained, albeit in a revised and somewhat expanded form. However, there are completely new sections on basic mathematics, ultrasonic measurements and patient safety. Although there is much to be admired in this book, it suffers from two major defects. The first arises from the authors' attempts to provide basic introductions to mathematics and to some, but not all, of the scientific concepts underlying the theory of the measurements which they later describe. It is interesting that, while they feel obliged to give potted summaries of mathematics, atomic theory, electricity and electromagnetism, they do not accord the same treatment to subjects such as Newtonian mechanics, fluid mechanics and acid–base chemistry, knowledge of which is equally important for our understanding of the measurement principle described later. It could well be that the authors have selected for discussion only those subjects which they find difficult; certainly, this interpretation is supported by the number of errors in these sections. For example, in the discussion of the concept of a function of x, $f(x)$, the authors interpret the function symbol "f" as a parameter by which x is multiplied. There are many other confusions of this sort in these background sections, with the result that they are of negligible value. It would surely have been better to have incorporated an early section stating the level of mathematical and scientific expertise required to understand the rest of the book, together with a summary of any important results and suitable references, and to have left it at that.

The second major defect is the inclusion of several topics which are really peripheral to the subject of clinical measurement, such as electronics, computers, ultrasonic and radionuclide imaging and statistics. Again, it would have been better to have given a short summary of the aspects of these subjects which are relevant to clinical measurement together with references. As they stand, these sections will convey little of value to the uninitiated readers at whom they are aimed.

There is also a lack of co-ordination between different sections of the book. Thus, a discussion of resonance and damping, together with several diagrams, appears in almost identical form in two different parts of the book and descriptions of Fourier series and exponential functions are similarly repeated after their first appearance.

On the positive side, most of the chapters on the subject of clinical measurement are clearly written and provide real insight into the principles of the measurements, and the potential errors to which they are subject. In particular, the chapters on intravascular pressure measurement and gas flow and volume measurement are especially well presented. Other excellent chapters are those on biological potentials, recorders, patient safety and blood-gas analysis. The high standard of these makes it all the more regrettable that the book is far bigger and more expensive than it need have been.

W. M. Gray

Anesthesia and the Patient With Endocrine Disease. Contemporary Anesthesia Practice. Edited by B. R. Brown, jr. Published by F. A. Davis Co./Philadelphia. Pp. 203; illustrated; indexed. Price £15 (approx.).

It is never a pleasant task to belittle a book which has obviously required effort and energy to produce. The text is disappointing, repetitive, inaccurate, pretentious and at times grandiose. Admittedly there is an excellent chapter by Professor Oyama on General Anaesthesia and Surgical Stress on Endocrine Function, and an authoritative chapter by Philbin and Coggins on The Effects of Anaesthesia on ADH, but thereafter it is impossible not to deliver a pejorative report.

The editing is erratic and seems to be confined to a series of irritating and patronizing platitudes before each chapter. There is a distinct lack of balance, as there are 80 pages devoted to the thyroid gland in a book of only 200 pages (three chapters out of a total of 13). The chapter by Dr Hellman could easily appear as a monograph in its own right. There are two chapters on the management of diabetes mellitus, one of which is superfluous and the other for no apparent reason interposed between the chapters on the thyroid. The detail of the formation of the thyroid hormone is churned out more than once, and contradictions abound. In one paragraph we are informed that "these theoretical considerations may be clinically important" while in the last sentence of the same paragraph it states, "The clinical significance of these changes is not clear at present." The reason for this may be that the paragraph extends onto two pages! The use of the cross-reference is conspicuous by its absence, with the result that the physiology of ADH is presented in different chapters. On one occasion we are told, "It is believed to be formed in the supraoptic nucleus", while in the other chapter we are told, "It is formed in the supraoptic nuclei."

The discussion on the management of diabetes is singularly unhelpful, and although "the patient should be evaluated carefully", there is no reference to electrolyte loss, sodium chloride, potassium, and how to treat dehydration. There are no references to DPG, while non-ketotic hyperosmolar diabetic coma is given scant attention. Ketosis is considered almost as an afterthought and is treated "more rigorously".

There is an obvious misprint in Whipple's triad, when the blood glucose is stated to be less than 50d/L. Presumably this is meant to be 50 mg/dl. The management of insulinoma reflects the author's obsession with blood sugars (the text refers to these as blood glucoses). It should not be necessary to tell us twice on one page to take samples of blood before induction of anaesthesia, to make sure that there is adequate transport to take the samples to the laboratory, to tell us that the laboratory should make their measurements urgently, and that there should be a chemical pathologist who understands the significance of hypoglycaemia!

There are numerous other inaccuracies and inconsistencies. The last chapter, written by the Editor, on Anaesthesia for Phaeochromocytoma, can only sport eight references, of which the latest is 1970. The account of metabolism of catecholamines detailed here differs markedly from that in Goodman and Gilman (1980). Dr Brown is convinced that pre-existing hypovolaemia causes the hypotension following removal of the phaeochromocytoma. He presents no data to support this assertion; in one of the scanty lists of his own references at the end of the chapter, careful reading will show "that the majority have normal blood and plasma volume". In the suggested anaesthetic technique for the removal of the tumour, anaesthesia is maintained with "enflurane–nitrous oxide". Oxygen is not mentioned. Perhaps this is what is lacking in the book.

Leon Kaufman

Diagnosis and Non-Surgical Management of Chronic Pain. By Nelson Hendler. Published by Raven Press, New York. Pp. 246; illustrated; indexed. Price $38.76.

In the preface to this book, the author states that it is a much more technical companion piece to a previously published volume written for the general public. This provides a key to why the book falls far short of the level at which it should have been written for its intended readers—the treating professionals as Dr Hendler calls them.

Dr Hendler sets out to provide guidelines for understanding and diagnosing chronic pain patients with particular emphasis on the psychological aspect of disease and treatment.

Although much of what he opines is of value, it has been written before, often with greater clarity and brevity. After a time, repetition becomes irksome and this is exemplified in the first 12 chapters of this book, which could be easily and profitably condensed into a review article, thus greatly benefitting the reader.

Chapter 13 deals with Psychological Tests for Chronic Pain Patients and, apart from some notable omissions, one is again left wondering just what the author has been trying to say by the end of the chapter. This represents a lost opportunity to review usefully the multiplicity of available tests and give a *resumé* of their respective values to the clinician.

Chapter 14 on the Psychopharmacology of Chronic Pain deals with this expanding topic in such a superficial and fragmented manner to make it, at best, inadequate and misleading. This trend is continued in the chapter dealing with the Anatomy of Pain, where endorphins and enkephalins are dealt with in nine lines, catecholamines in five and substance P in eight!

The remaining chapters on Alternative Treatment, Organisation of a Treatment Centre and Physician Reaction to Patients may mirror current practice in U.S.A., but certainly would not be in line with contemporary trends in the U.K. and Europe.

This is not a book one can recommend strongly to any particular group. However, the well-printed pages contain some valuable lessons.

K. Budd

Anaesthesiology, ICS 538. Edited by E. Rugheimer, and M. Zindler. Published (1981) by Excerpta Medica, Amsterdam. Pp. 1068; illustrated; indexed. Price $155.50.

This volume represents something approaching an editorial and publishing miracle, being the Proceedings of the 7th World Congress of Anaesthesiologists held only last September. The Editors have been selective in the material that is presented. The guest lectures which preceded each day's programme have been highlighted, as have the main symposia. While there continues to be controversy on the value of the publication of proceedings, this volume must surely represent the best that can be achieved and will constitute an accurate record of the best of what was available at Hamburg. At a cost of $155.50 it is unlikely to be attractive for personal collections.

Alastair A. Spence

Aids to Anaesthesia. 1: The Basic Sciences. By M. J. Harrison, T. E. J. Healy and J. A. Thornton. Published by Churchill Livingstone. Pp. 216; illustrated; indexed. Price £5.95.

This book is intended to help candidates in the final preparation for postgraduate examinations in the basic sciences for anaesthesia. It makes a brave attempt to be comprehensive—at least for the primary F.F.A.R.C.S. examination—and includes sections on physics, clinical measurement, physiology and pharmacology.

For such a short text, to cover such an enormous field is a difficult task and, of necessity, this book is composed of lists and headings with very few subjects covered in depth and no references or guides to further reading. However, there is much useful information which is easily accessible for it is well laid out, illustrated and indexed.

The authors state that they have not included all the knowledge required to pass the examination and that the book is an *aide-memoire.* In this rather limited field it deserves to be successful and is recommended as additional reading for those sitting F.F.A.R.C.S. examination.

W. S. Nimmo

Isoflurane (*Forane*). A compendium and reference written by Edmond I. Eger, II. Published by Ohio Medical Products, 3030 Airco Drive, P.O. Box 7550, Madison, Wisconsin 53707. Pp. 110; illustrated. Available on request from publisher.

Isoflurane has recently been released for clinical use in the United States and this splendid publication is a compendium and reference volume on the drug. Apart from being a very scholarly contribution on isoflurane there are invaluable comparative data on the other commonly used inhalation anaesthetics, making this book a very worthwhile addition to the library. Given the skill in writing and the quality of the production it is a pity that there is no index. Ohio Medical Products and Dr Eger are to be congratulated in making a splendid contribution to the educational literature of anaesthesia.

A. A. Spence

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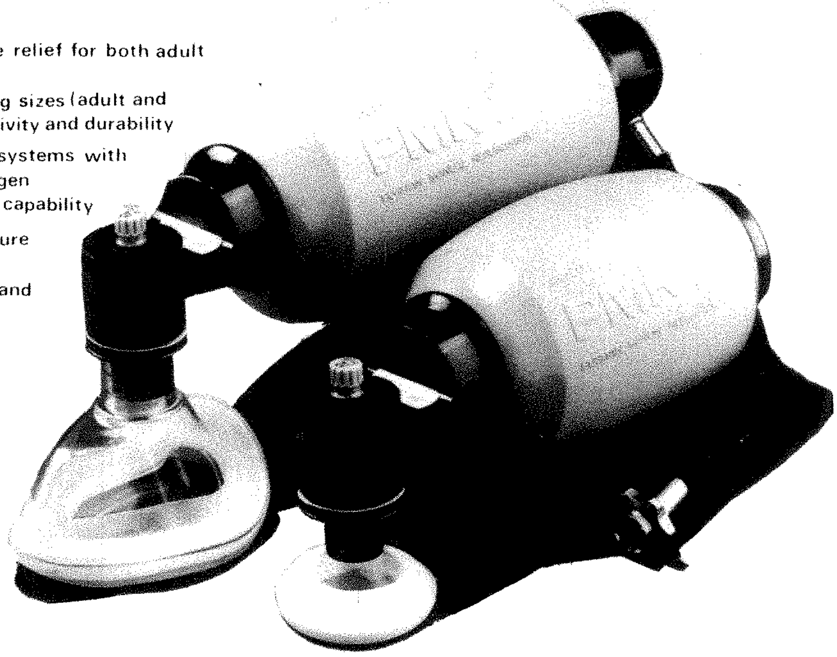

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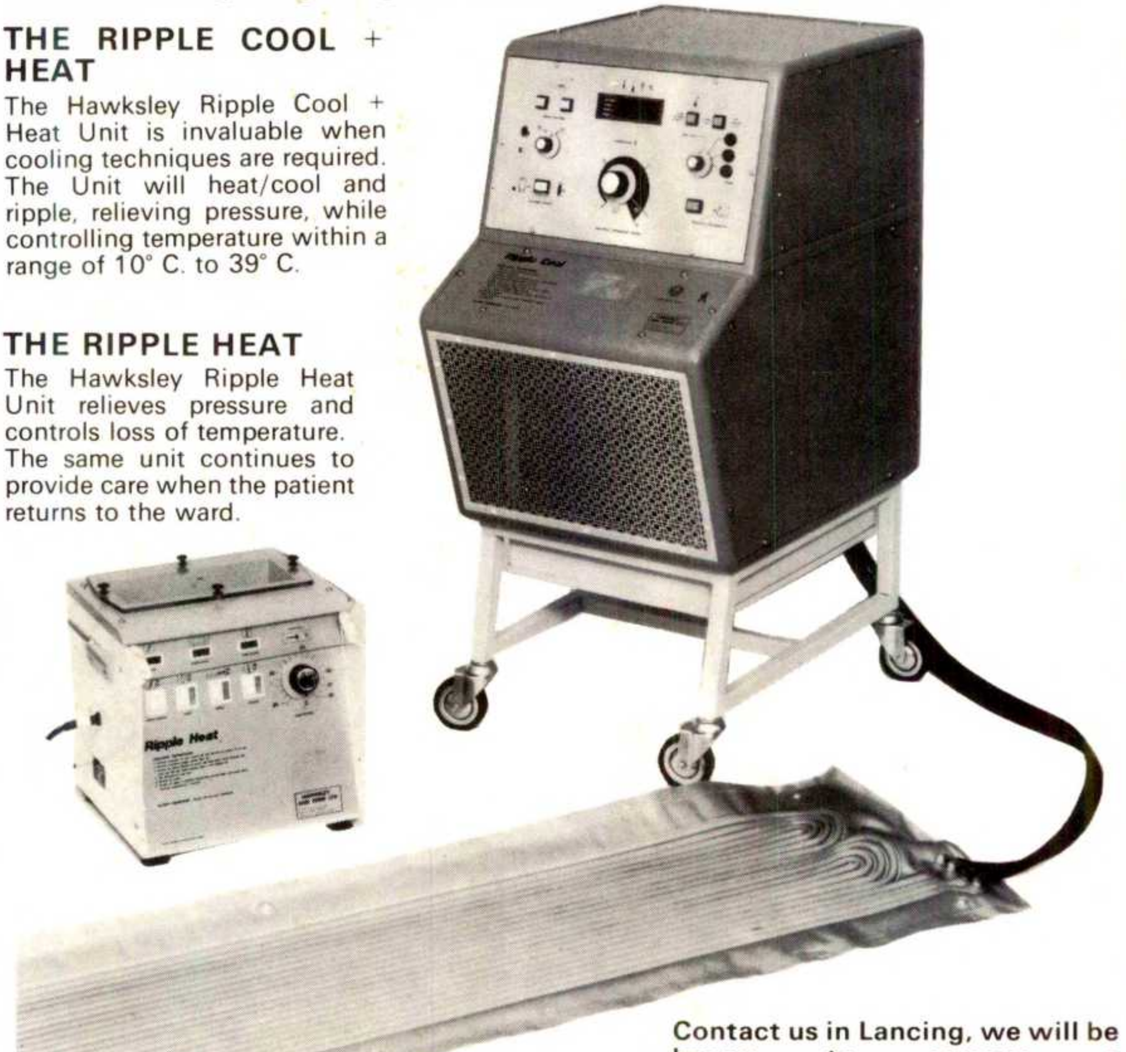

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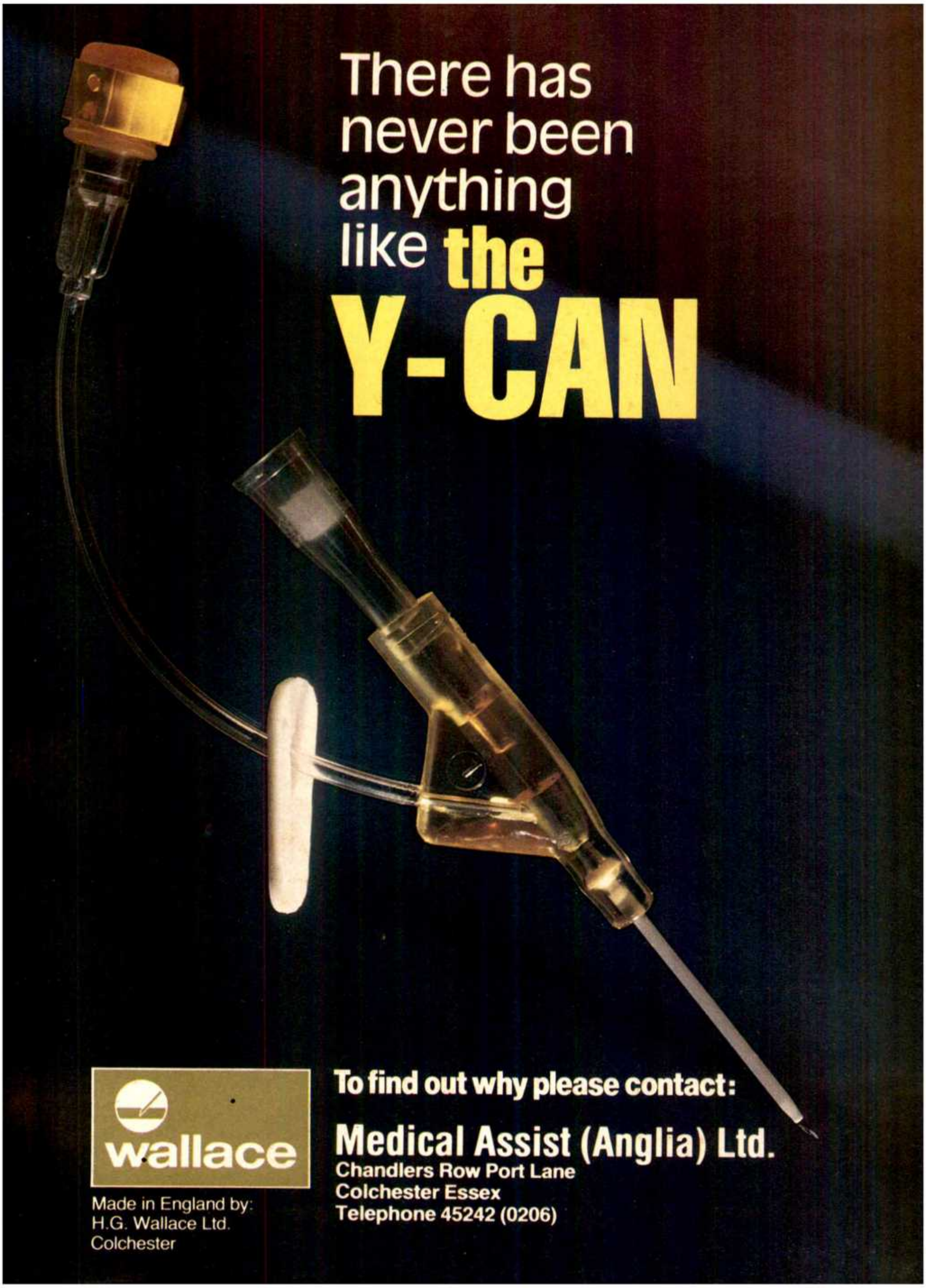

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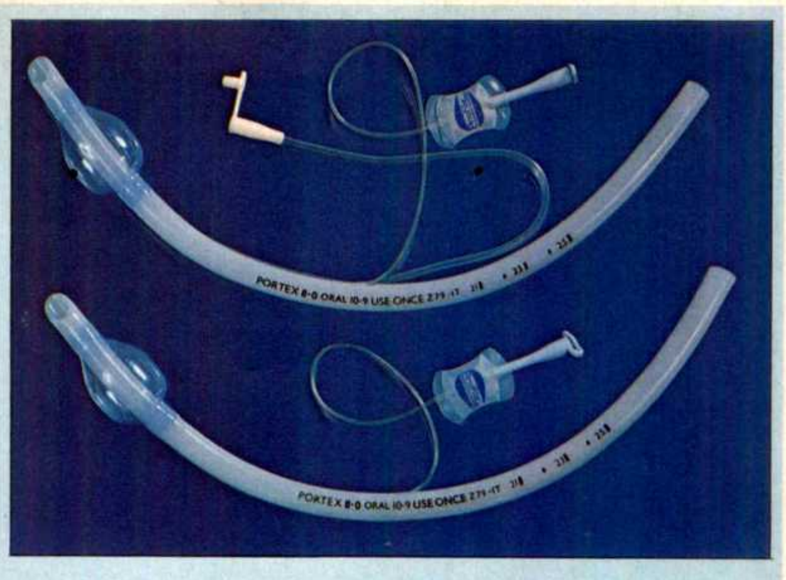

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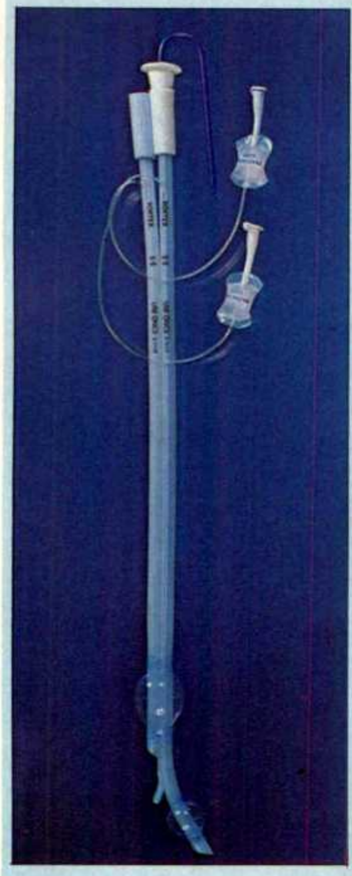

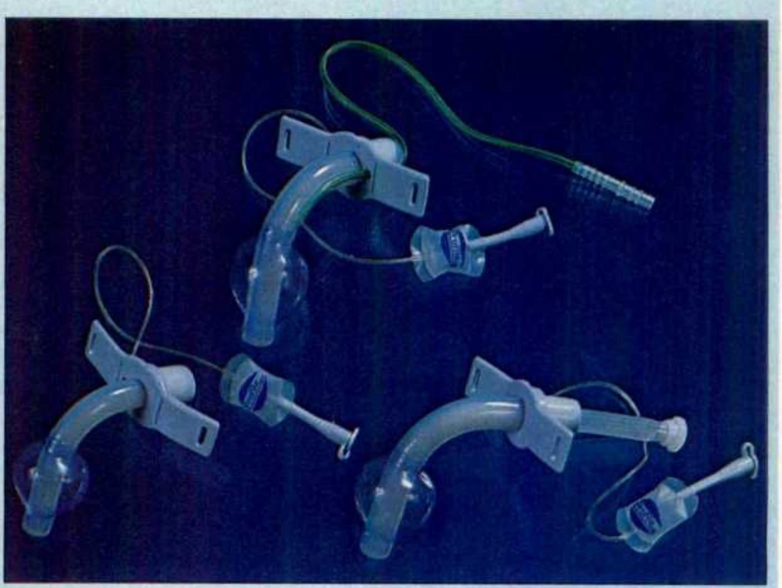

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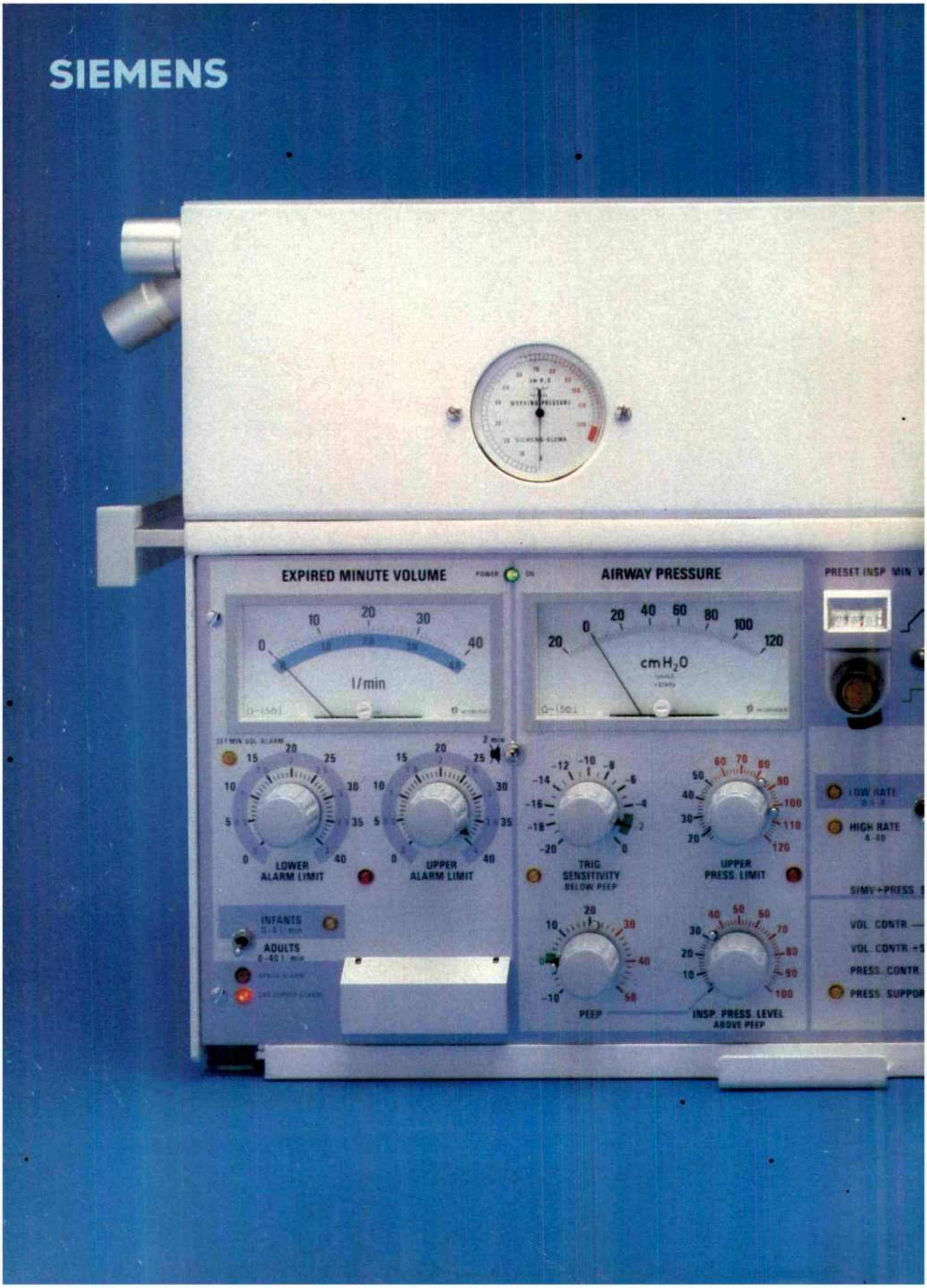

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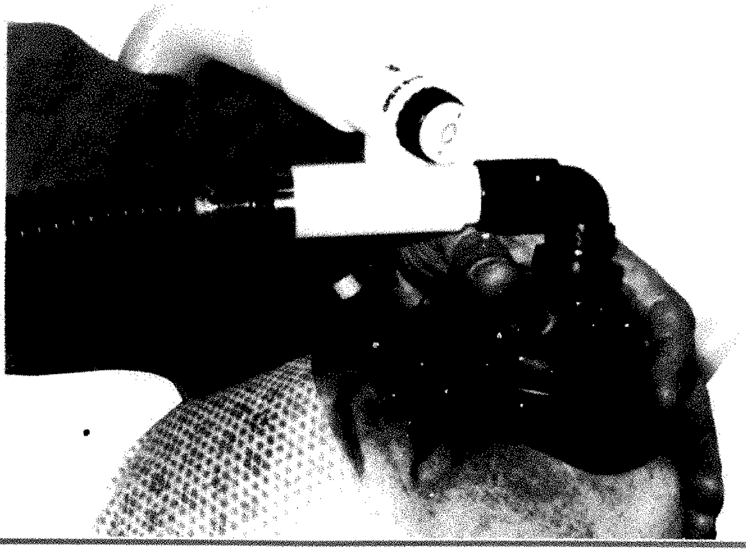

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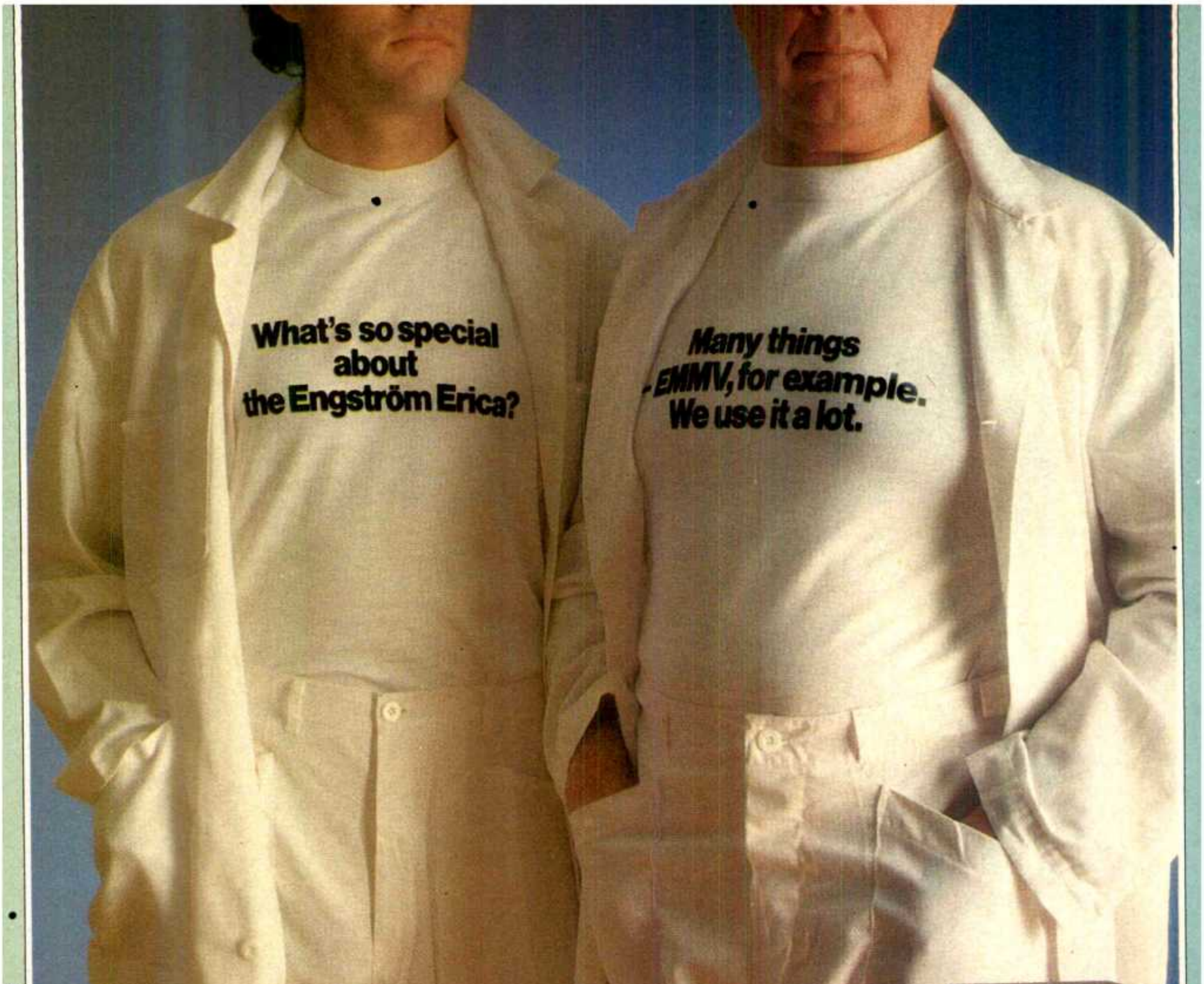
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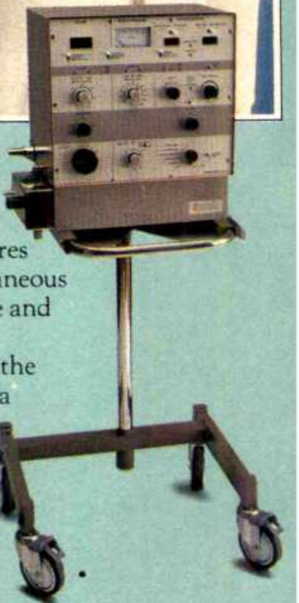

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

ISOFLURANE

The introduction to clinical practice of a new volatile anaesthetic is a rare and notable event nowadays. Isoflurane has recently been released for general use in the U.S.A. and Canada 16 years after its original synthesis by Ross Terrell in 1965.

Isoflurane, the structural isomer of enflurane, was developed as one of a series of fluorinated methyl-ethyl ethers (Vitcha, 1971) which were considered likely to produce a non-inflammable anaesthetic balanced in favour of anaesthetic action rather than convulsant properties. It was almost abandoned as a commercial project because of difficulties in separating isoflurane from contaminants produced during its manufacture. Following human trials of both enflurane and isoflurane (Virtue et al., 1966; Dobkin et al., 1968; Homi et al., 1972; Stevens et al., 1971) it appeared that isoflurane was preferable to the existing volatile and gaseous anaesthetics and it was scheduled for release in 1975. However, the results of a study by Corbett (1976), suggesting a carcinogenic potential for isoflurane, were publicized in the popular press and the agent was hurriedly withdrawn. Corbett supported his findings with speculations that the carcinogenic effect of isoflurane could be related to its α-chloroether structure. Some other α-chloroethers are potent carcinogens, but are also highly reactive and biodegradable. Isoflurane is physically stable and minimally susceptible to biodegradation. Subsequent studies using the Ames test and sister chromatid exchange test failed to demonstrate any mutagenic effects of isoflurane (Baden et al., 1977; Waskell, 1978; White et al., 1979) and extensive studies have failed to demonstrate any teratogenic potential of isoflurane.

A further extensive study (Eger et al., 1978), designed to eliminate some of the observer bias in Corbett's study, showed that isoflurane was not carcinogenic. It is interesting to note that the mice used in Corbett's 1975 study were fed with animal foodstuffs contaminated with polybrominated biphenyls following an episode of foodstuff contamination in the State of Michigan. Polybrominated biphenyls have been shown to be powerful teratogens and mutagens (Corbett et al., 1975) and could have been responsible for the hepato-carcinogenic effects in Corbett's mice.

Isoflurane has many physical properties in common with its isomer enflurane, but its lower solubility in blood and tissues allows a more rapid uptake, distribution and elimination than other available volatile agents and thus both the onset and recovery from isoflurane anaesthesia are rapid (Cromwell et al., 1971). Isoflurane, to a slightly greater degree than halothane, but to a lesser degree than enflurane, profoundly depresses ventilation in a dose-dependent manner (Fourcade et al., 1971) although nitrous oxide or surgical stimulation can limit this impairment of ventilation (Eger et al., 1972; France et al., 1974).

By contrast, the effects of isoflurane on the cardiovascular system are more advantageous to the patient than those of either halothane or enflurane. Studies in animals (Horan et al., 1977a), human volunteers (Stevens et al., 1971) and patients (Tarnow et al., 1977) have all shown that, although isoflurane causes greater arterial hypotension than halothane and slightly less than enflurane at equipotent MAC values, stroke volume and cardiac output are considerably less impaired by isoflurane. Thus the main site of action of isoflurane is on the peripheral arteriolar system in that it reduces systemic vascular resistance (SVR) to a greater extent than enflurane (Calverley et al., 1978), whereas halothane exerts very little effect on SVR (Prys-Roberts et al., 1974). Isoflurane causes significantly less impairment of myocardial contractile performance than either enflurane of halothane, although the mechanism of its effect on the contractile proteins and their enzyme systems is similar to that of halothane (Pask, England and Prys-Roberts, 1981). Myocardial oxygenation is well maintained in the elderly human patient even though coronary blood flow is reduced in proportion to the decrease of myocardial work induced by the arterial hypotension (Tarnow et al., 1976). Isoflurane does not sensitize the conduction system of the heart to the effects of exogenous adrenaline and 3.5 times the dose of adrenaline can be tolerated during isoflurane compared with halothane anaesthesia (Johnston, Eger and Wilson, 1976). Similarly, the dysrhythmia threshold to increased Pa_{CO_2} is higher than with halothane (Joas and Stevens, 1971). Hypovolaemia is better tolerated during isoflurane anaesthesia than with either halothane or enflurane, and those effects were not altered by pre-existing beta-receptor blockade (Horan et al., 1977a, b).

The central nervous effects of isoflurane are comparable to those of other volatile agents in that cerebral blood flow and intracranial pressure are increased to a degree comparable to enflurane, but less than halothane. The electroencephalographic response to increasing concentrations of isoflurane is predictable with a change from a high frequency–low voltage activity at alveolar concentrations below MAC giving way to a low frequency–high voltage activity during light surgical anaesthesia (1–1.5 MAC) and a progression to burst suppression at deeper levels of anaesthesia (Homi et al., 1972). Unlike its isomer enflurane, isoflurane does not induce epileptiform e.e.g. activity, nor can such activity be evoked by hyperventilation to low Pa_{CO_2} values.

In a climate of increasing concern about the metabolism of volatile anaesthetics and the relationship to toxic effects of potential or real metabolites, the minimal metabolism of isoflurane is notable. Less than 0.2% of the isoflurane taken up by the body can be recovered as metabolites (Holaday et al., 1975), and the serum fluoride concentrations are comparable to those found after halothane anaesthesia and significantly less than those found after enflurane or methoxyflurane anaesthesia (Mazze, Cousins and Barr, 1974). Two pathways of oxidative metabolism of isoflurane have been proposed, which largely account for the observed renal excretion of fluoride metabolites, but neither pathway produces potentially toxic metabolites. A reductive pathway which could occur under hypoxic conditions has been proposed but has not been confirmed. Induction of the mixed oxidase microsomal enzyme system of the liver has much less effect on isoflurane metabolism compared with either enflurane or methoxyflurane. Thus the lack of liver dysfunction observed in man and animals after isoflurane anaesthesia is consistent with the physical stability and resistance to biodegradation of this agent.

The process to register isoflurane under E.E.C. regulations is already under way and the anaesthectic may become available here within a year. What future exists in the United Kingdom for the introduction of isoflurane as an alternative to other volatile agents? Is there a need for a variety of anaesthetics, and does their increased cost of administration justify their widespread use? There is no doubt that enflurane has had a limited impact on anaesthesia in this country, compared with the overwhelming move away from halothane, fluroxene and methoxyflurane to enflurane in the U.S.A. Clearly isoflurane has distinct advantages over both enflurane and halothane, and one wonders whether any market would have existed for enflurane had isoflurane been released in 1975. One consequence of the introduction of enflurane in the meantime, has been the costly exercise of equipping anaesthetic machines with enflurane vaporizers. How will the cost of introducing isoflurane compare with that of enflurane? Both enflurane and isoflurane are considerably more expensive to administer than halothane. Allowing for the different equipotent concentrations and current prices for the agents, enflurane is more than seven times as expensive as halothane, and isoflurane over 10 times as expensive as halothane. Are the undoubted advantges of isoflurane worth the cost? Time alone will tell.

C. Prys-Roberts

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A METHOD FOR ACHIEVING RAPIDLY STEADY-STATE BLOOD CONCENTRATIONS OF I.V. DRUGS*

J. R. A. RIGG AND T. Y. WONG

SUMMARY

The theoretical basis of a pharmacokinetic method to obtain rapidly and maintain a steady plasma concentration of an i.v. drug is described. Computer simulations of morphine disposition in man, using pharmacokinetic constants obtained from the literature, are provided as examples of steady-state dose regimens. The usefulness and potential limitations of the method are discussed.

A basic assumption of the concept of "MAC"—the minimum alveolar concentration required to obtund the motor response of 50% of patients to a standard surgical incision—is that steady-state inhalation anaesthesia occurs with steady-state brain anaesthetic concentration. On the other hand, non-volatile anaesthetic drugs are usually given by intermittent i.v. injection, and as a result, there are wide fluctuations of blood and brain drug concentrations and the "level" of anaesthesia (Berkowitz et al., 1975; Murphy, Olson and Hug, 1979). This may explain why the use of narcotics, for example, may be associated with inadequate anaesthesia or analgesia and awareness during anaesthesia on the one hand, or unwanted effects such as nausea, vomiting, and postanaesthesia respiratory depression on the other hand (Rigg et al., 1978; Stapleton, Austin and Mather, 1979).

It seems logical, therefore, to use a more precise method of giving parenteral drugs to maintain a steady state of anaesthesia and analgesia.

This paper describes a theoretical analysis of a general method of infusing drugs to provide a steady-state concentration in the plasma. The method is a modification of the approach of Vaughan and Tucker (1976). These authors described a derivation of the ideal i.v. drug input required to achieve and maintain a constant plasma drug concentration. The results of computer simulation studies, using data from morphine obtained from the literature (Berkowitz et al., 1975), are described. Morphine was chosen for two reasons. First, it has been the subject of extensive pharmacokinetic analysis in animals and man, and its disposition is known to be consistent with an open two-compartment model with first-order drug elimination from the central compartment (Catlin, 1977). Second, morphine is widely used in medical, surgical and anaesthetic practice and the analysis is pertinent to all of these. In a companion paper, application of the method is described in experiments using fentanyl in the anaesthetized rabbit (Rigg et al., 1981).

The clinical objectives of general anaesthesia are rapid smooth induction, avoidance of toxicity and maintenance of a smooth plateau of surgical analgesia. The corresponding pharmacokinetic objectives of the method described here are to achieve steady-state plasma concentration (C_p^{ss})as quickly as possible and to place strict limits on deviations from the selected plasma concentration. In the present paper, a limit of ±20% C_p^{ss} achieved within 2 min of beginning morphine, was chosen.

THEORY

To clarify the rationale of combining a bolus injection with two or more consecutive constant infusions, pharmacokinetic theory is presented in four parts: (a) bolus injection, (b) constant-rate infusion, (c) combination of bolus injection with a

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single constant-rate infusion and (d) combination of bolus injection with more than one constant-rate infusion.

(a) Bolus injection

If a single dose d of a drug is injected i.v., C_p at time t, according to the two-compartment open model, will be given by the following equation:

$$C_p = A\,e^{-\alpha t} + B\,e^{-\beta t} \text{(fig. 1)} \qquad (1)$$

where

$$A = \frac{Xd(\alpha - k_{21})}{V_1(\alpha-\beta)}$$

$$B = \frac{Xd(k_{21}{}^{-\beta})}{V_1(\alpha-\beta)}$$

$$V_1 = \frac{Xd}{A+B}$$

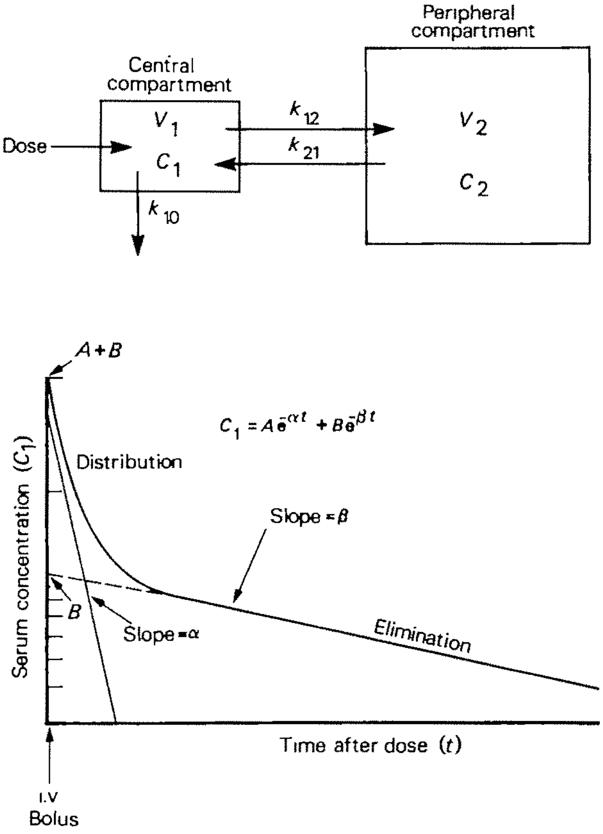

FIG. 1. Schematic representation of the open two-compartment model, the plasma concentration–time relationship and the biexponential expression describing that relationship.

(b) Constant-rate infusion

If a constant-rate infusion, Q, is established, C_p at any time t after initiation of infusion is given by the equation (Greenblatt and Koch-Weser, 1975):

$$C_p = \frac{Q}{V_1 k_{10}}\left[1 + \frac{(\beta - k_{10})}{\alpha-\beta}e^{-\alpha t} + \frac{(k_{10}-\alpha)}{\alpha-\beta}e^{-\beta t}\right] \qquad (2)$$

When it is sufficiently large, C_p will reach a steady-state C_p^{ss}, where $C_p^{ss} = Q/V_1\,k_{10}$, which is independent of time. However, the establishing of a desired C_p^{ss} using a single constant-rate infusion will take many hours. To overcome this problem, Wagner (1974) proposed a consecutive two rate-constant infusion method, to achieve C_p^{ss} more rapidly. However, this method may necessitate an unacceptably long delay after beginning the infusion, before C_p^{ss} is achieved.

(c) Combination of bolus injection and single constant-rate infusion

Equations (1) and (2) are graphically represented in figures 2 and 3, using the data of Berkowitz and others (1975), for morphine. These figures show an exponential decrease following i.v. bolus injection, and an exponential increase associated with constant-rate infusion, of drug concentration with time. Intuitively, it seems that combining these two approaches may achieve C_p around C_p^{ss}. The single loading dose Xd required to achieve C_p^{ss}, almost instantaneously, is:

$$Xd = C_p^{ss}\,.\,V_1 \qquad (3)$$

The constant infusion rate, Q^{ss}, that will achieve C_p^{ss} eventually is:

$$Q^{ss} = C_p^{ss}\,.\,V_1\,.\,k_{10} \qquad (4)$$

If this loading dose is combined with this constant infusion (Boyes et al., 1971), C_p at any time t is given by:

$$C_p = Q^{ss}/V_1\,k_{10} + Fe^{-\alpha t} + Ge^{-\beta t} \qquad (5)$$

where

$$F = \frac{(\alpha Xd - Q^{ss})(k_{10}-\beta)}{V_1\,k_{10}(\alpha-\beta)} \qquad (6)$$

and

$$G = \frac{(\beta Xd - Q^{ss})(\alpha - k_{10})}{V_1\,.\,k_{10}(\alpha-\beta)} \qquad (7)$$

From equation (5) it can be seen that C_p is not constant as t changes. However, when t is very

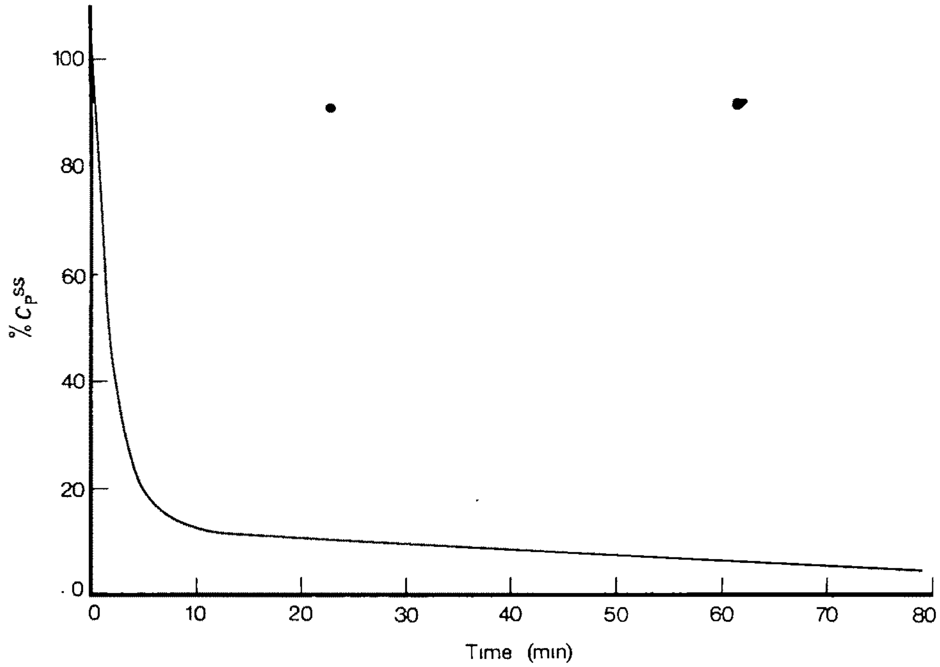

FIG. 2. Computer-predicted plasma concentration–time relationship for morphine after bolus dose, *X*d at time $t = 0$. Prediction based on data of Berkowitz and others (1975).

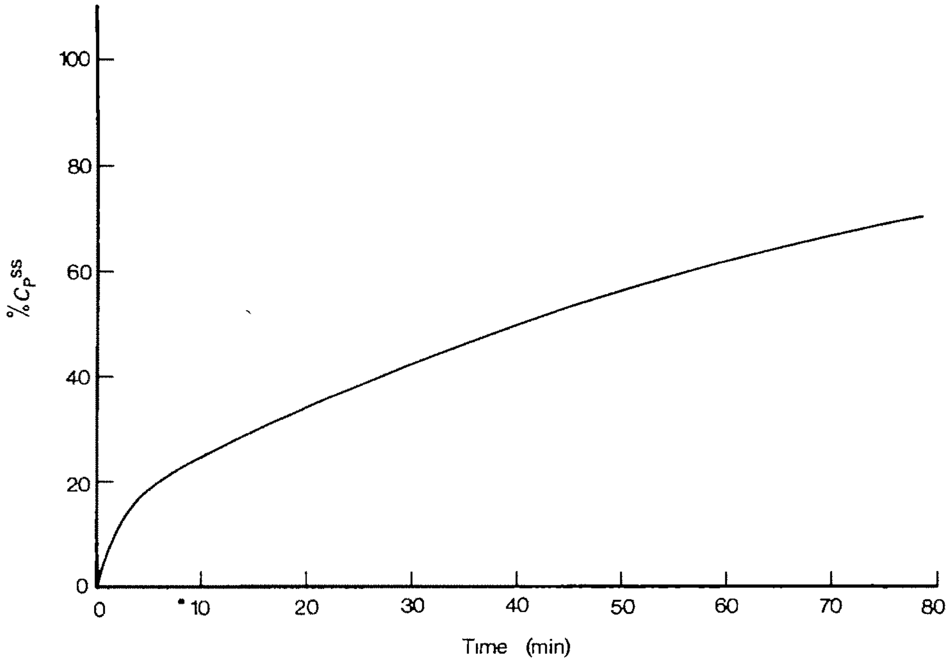

FIG. 3. Computer-predicted plasma concentration–time relationship for morphine after constant-rate infusion beginning at time $t = 0$. Prediction based on data of Berkowitz and others (1975).

large, $e^{-\alpha t}$ and $e^{-\beta t}$ approach 0 and C_p will approximate $Q^{ss}/V_1 k_{10}$ (that is, C_p^{ss}).

A typical curve for morphine, from the data of Berkowitz and others (1975) described by equation (5), is shown in figure 4. In this example, C_p decreases to 35% of C_p^{ss} at $t = 7.5$ min, at which moment it begins to increase again, reaching 80% of C_p^{ss} at 100 min. Clearly, such a curve exceeds the predetermined limit of ±20% C_p^{ss}.

Intuitively, it seems possible that this problem might be overcome by the procedure of Mitenko and Ogilvie (1972) who proposed a larger loading dose:

$$Xd = C_p^{ss} . V^\beta \qquad (8)$$

where

$$V^\beta = V_1 . k_{10}/\beta$$

Mitenko and Ogilvie (1972) combined this loading dose with the constant-rate infusion, Q^{ss}, a procedure that they showed to be relatively safe for theophylline. When this large loading dose is substituted in equation (5), the term G equals 0, and C_p will never decrease to less than C_p^{ss} (fig. 5). However, morphine and most other lipid-soluble anaesthetic drugs are distributed extensively into a peripheral compartment. This causes a relatively high ratio of initial to steady-state plasma concentration ($C_p^0 : C_p^{ss}$; for Berkowitz and others' (1975) morphine data = 6.3 : 1). Consequently, an unacceptably high initial C_p may occur, as is evident in figure 5.

The effect of a loading dose for morphine, intermediate between the two values described by equations (3) and (8), is shown in figure 6, which shows predicted concentration–time profiles when Q^{ss} is combined with three different bolus doses: (1) $Xd = 1/2 \; C_p^{ss} . (V^\beta + V_1)$; (2) $Xd = 1/3 \; C_p^{ss} . V^\beta$ and (3) $Xd = 1/6 \; C_p^{ss} . V^\beta$. None of these curves is satisfactory. Either C_p is too great initially, or too small before C_p^{ss} is obtained.

(d) Combination of loading dose with more than one consecutive constant-rate infusion

The computer simulated curves of figure 6 substantiate the prediction of Kruger-Thiemer (1968) that, for a system with more than one compartment, a desired blood concentration cannot be achieved rapidly and maintained by any choice of a single i.v. loading dose and a single constant infusion rate. More recently, Vaughan and Tucker (1976) described a general method for ideal drug input to achieve rapidly and maintain a desired C_p^{ss}. Their method incorporates a loading

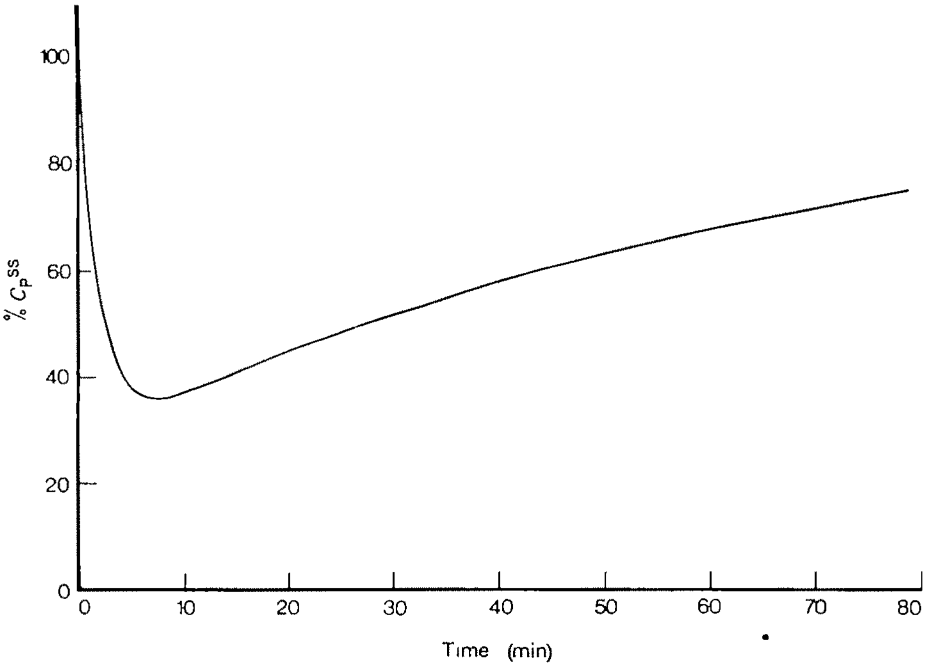

FIG. 4. Computer-predicted plasma concentration–time relationship for morphine after bolus dose, Xd, and constant-rate infusion beginning at time $t = 0$. Prediction based on data of Berkowitz and others (1975).

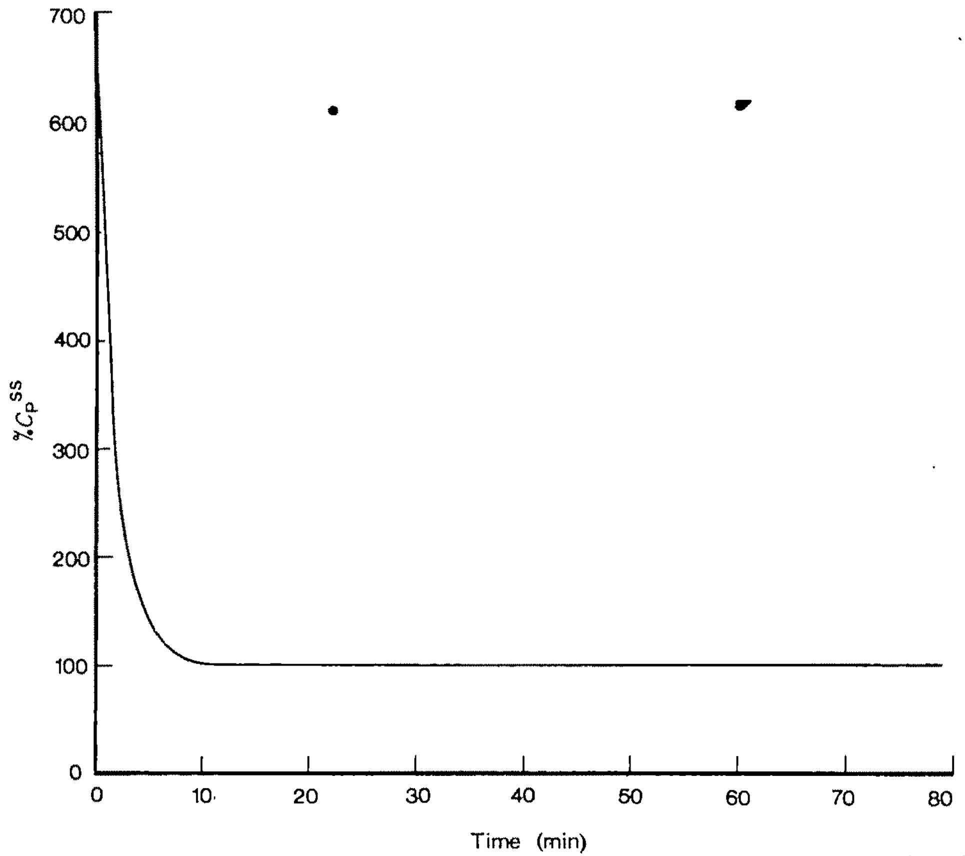

FIG. 5. Computer-predicted plasma concentration–time relationship for morphine using the procedure of Mitenko and Ogilvie (1972), for combined bolus and constant-rate infusion doses. Prediction based on data of Berkowitz and others (1975).

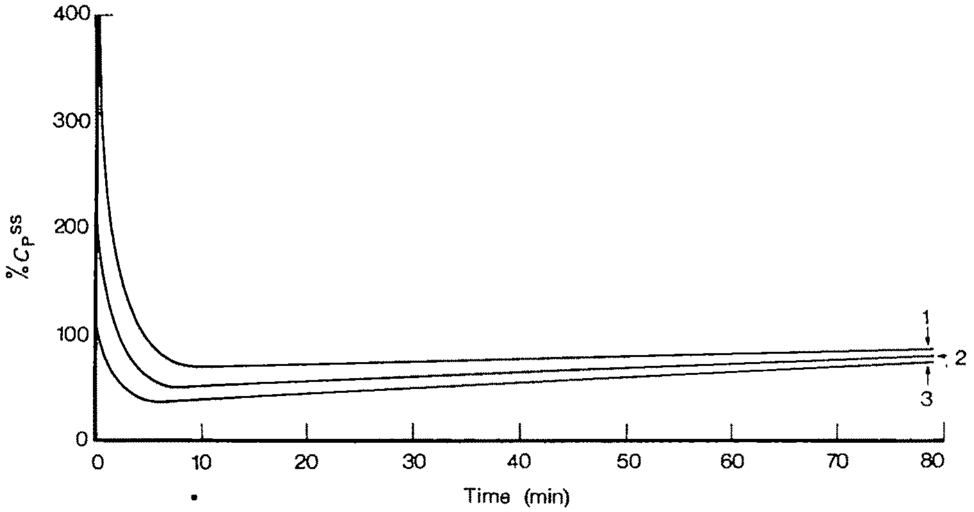

FIG. 6. Computer-predicted plasma concentration–time relationship when a constant-rate infusion is begun with three different bolus doses, intermediate in magnitude to those calculated by the methods of Boyes and others (1971) (fig. 4) and Mitenko and Ogilvie (1972) (fig. 5). Predictions based on data of Berkowitz and others (1975). See text for further details.

dose Xd (equation (3)), a constant rate infusion (equation (4)) and an infusion rate exponentially decreasing with time according to the following expression:

$$Qe = XdU_1 . k_{21} . e^{-k_{21}t} \qquad (9)$$

where

$$U_1 = (\alpha - k_{21})(\beta - k_{21})^2.$$

The plasma concentration, C_{Pe} resulting from the exponential infusion Qe is given by the convolution integral:

$$C_{Pe} = Qe(t)^{\star} \sum_{i=1}^{2} A_i . e^{-\alpha_i t} \qquad (10)$$

$$= \int_0^t Qe(\tau) A_i e^{-\alpha_i(t-\tau)} d\tau \qquad (11)$$

where

$$\sum_{i=1}^{2} A_i e^{-\alpha_i t}$$

is the response of the two compartment system to a unit impulse input and

$$A_1 = \frac{(\alpha - k_{21})}{V_1(\alpha - \beta)}$$

and

$$A_2 = \frac{(k_{21} - \beta)}{V_1(\alpha - \beta)} . A_1, \; A_2, \; \alpha_1 \text{ and } \alpha_2$$

are notations used by Vaughan and Tucker and are related to parameters used in this paper, as follows:

$$A_1 = \frac{A}{Xd}; \; A_2 = \frac{B}{Xd}, \; \alpha_1 = \alpha \text{ and } \alpha_2 = \beta$$

With Qe(τ) substituted by equation (9), and after integration and simplification, equation (11) becomes:

$$C_{Pe} = \frac{Xd(\alpha - k_{21})(k_{21}{}^{-\beta})}{V_1 . k_{21}(\alpha - \beta)} . (e^{-\beta t} - e^{-\alpha t}) \qquad (12)$$

Since $C_P{}^{ss} = Q^{ss}/V_1 . k_{10}$, $Q^{ss} = Xdk_{10}$, and $k_{10} = \alpha\beta/k_{21}$, equation (5) can be simplified to:

$$C_P = C_P{}^{ss} + \frac{Xd(\alpha - k_{21})(k_{21} - \beta)}{V_1 k_{21}(\alpha - \beta)} . (e^{-\alpha t} - e^{-\beta t}) \qquad (13)$$

The sum of equations (12) and (13) is $C_P{}^{ss}$. Hence, the plasma concentration attributable to the loading dose Xd (equation (3)), the constant-rate infusion Q^{ss} (equation (4)) and an exponential infusion (equation (9)), combined, is $C_P{}^{ss}$ at all times. In other words, a steady plasma concentration can be obtained almost instantaneously and maintained indefinitely by a combination of these three doses. An exponentially decreasing infusion rate could be provided by a specially designed pump. However, this approach is not favoured by us because of the increased difficulties for the clinician in conceiving quantitatively both dose and rate of dosing with a system incorporating an infusion rate that is continually changing. To overcome this problem, the exponentially decreasing infusion rate may be approximated by a series of fixed duration sequential constant rate infusions.

Since the rate of exponential infusion at time $t = XdU_1 . k_{21} . e^{-k_{21}t}$, the cumulative infusion from time $t = 0$ to time t is:

$$\int_0^t XdU_1 . k_{21} . e^{-k_{21}\tau} d\tau = XdU_1(1 - e^{-k_{21}\tau}) \qquad (14)$$

The cumulative infusion time curve has the general features given by the plot of $1 - e^{-k_{21}\tau}$ $v.$ time (fig. 7). This curve can be approximated by any number of sequential linear segments; the greater the number, the more closely the series of linear functions approximates the exponential function. In figure 7, four segments are chosen to approximate the curve of four consecutive time periods. Each successive infusion rate is a function of the slope of corresponding successive segments of the exponential curve. For example,

Q_1e = Slope $S_1 . (-XdU_1)$, infusion rate, given from time 0 to t_1
Q_2e = Slope $S_2 . (-XdU_1)$, infusion rate, given from time t_1 to t_2
Q_3e = Slope $S_3 . (-XdU_1)$, infusion rate, given from time t_2 to t_3
Q_4e = Slope $S_4 . (-XdU_1)$, infusion rate, given from time t_3 to t_4

APPLICATION

The method was tested by computer simulation. A computer program (VANDT, Fortran IV, CDC 6400) was written to permit calculation of a dosage schedule based upon known pharmacokinetic parameters. The desired $C_P{}^{ss}$ and the maximum allowable fluctuation from $C_P{}^{ss}$,

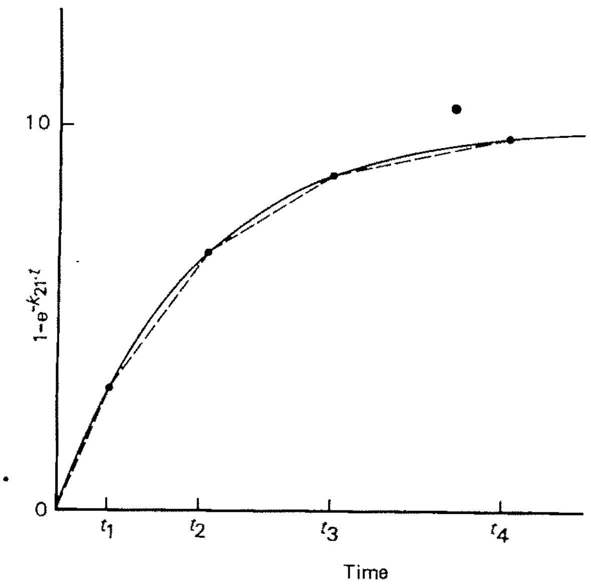

FIG. 7. The cumulative infusion time curve described by Vaughan and Tucker (1976) (continuous line) and its approximation by four consecutive straight lines, representing four successive different constant rate infusions. See text for further details.

expressed as a percent of C_p^{ss}, are specified. Infusion times $t_1, t_2 \ldots$ may be specified or the computer may be instructed to specifiy the most appropriate times. The least number of infusions required is determined. The program prints out loading dose, Xd, infusion rates Q_1, Q_2, etc., the duration of these infusions, maximum deviations (as % C_p^{ss}) and the times that these deviations occur.

Computer simulation studies were conducted using the data of Berkowitz and others (1975) for morphine (table I). A limit of $\pm 20\%$ C_p^{ss} was set; this was considered well within the limit of clinical efficacy and safety, yet large enough to permit attainment of a specified C_p^{ss} value with only two consecutive infusions. An infusion time of 15 min for the first infusion was determined as being optimum for providing C_p^{ss} within the selected limit, when followed by the calculated steady-state infusion rate. That is, after the bolus, Q_1 would be infused from 0 to 15 min, Q_2 from 15 min for as long as required.

Suppose C_p^{ss} = morphine $400\,\mathrm{ng\,ml^{-1}}$ is selected. Substituting in equation (3):

$$Xd = C_p^{ss} . V_1 = 0.65\,\mathrm{mg\,kg^{-1}}$$

$$Q_1e = -XdU_1 . S_1 = 0.0138\,\mathrm{mg\,kg^{-1}}$$

TABLE I. *Pharmacokinetic parameters of individual subjects and pooled data of subjects of Berkowitz and others (1975)*

Subject	A (g ml^{-1})	α (h^{-1})	B (g ml^{-1})	β (h^{-1})
1	0.4637	−20.57	0.1109	−0.5377
2	0.2052	−16.55	0.08653	−0.5347
3	0.4323	−20.86	0.08741	−0.5503
4	1.1029	−47.50	0.11702	−0.8747
5	1.1284	−45.65	0.13712	−0.9452
6	0.4404	−32.87	0.10603	−0.7260
7	1.1139	−24.77	0.20758	−1.3639
8	1.1429	−45.79	0.10410	−0.9486
9	0.1185	−9.417	0.08428	−0.6174
10	1.5652	−36.24	0.12019	−1.1092
11	0.6226	−20.73	0.10078	−0.9838
12	0.9618	−25.37	0.1496	−0.4963
13	1.4863	−47.24	0.2101	−1.1473
14	1.8782	−44.05	0.1201	−0.7685
15	0.5288	−12.30	0.09615	−0.4861
16	0.4783	−19.02	0.08479	−0.1908
17	0.2698	−32.33	0.1210	−0.8134
18	3.1852	−67.55	0.1292	−1.0291
Pooled	0.7652	−31.30	0.1214	−0.8033

From equation (4):

$$Q^{ss} = C_p^{ss} . V_1 k_{10} = 0.0055\,\mathrm{mg\,kg^{-1}\,min^{-1}}$$

Since Q_1e, and Q^{ss} are constant rate infusions, Q_1e and Q^{ss} are added to give a new constant rate infusion Q_1, and Q^{ss} becomes Q_2.

The final dose schedule is:

1: Xd $6.5\,\mathrm{mg\,kg^{-1}}$ given at $t = 0$

2: Q_1 $0.019\,\mathrm{mg\,kg^{-1}}$ given from 0 to 15

3: Q_2 $0.0055\,\mathrm{mg\,kg^{-1}}$ given from 15 min indefinitely.

Computations for $C_p^{ss} = 400$, 300, 200 and $100\,\mathrm{ng\,ml^{-1}}$ are plotted in figure 8. For each, the least deviation of C_p^{ss} was 82%, occurring at 3 min and the greatest deviation was 115% of C_p^{ss} at 15 min.

If more than two different consecutive constant-rate infusions are used, then the predetermined steady-state drug concentration can be simulated more precisely and a more narrow limit of fluctuation defined. Greater precision (lower predicted drug concentration fluctuations) can be achieved at the expense of simplicity (a larger number of consecutive infusions will be required). The computer program requires the pharmacokinetic model parameters and the preselected drug concentration and fluctuation limits. Given this information, the program prints out the least number of infusions required to maintain C_p^{ss} within this limit.

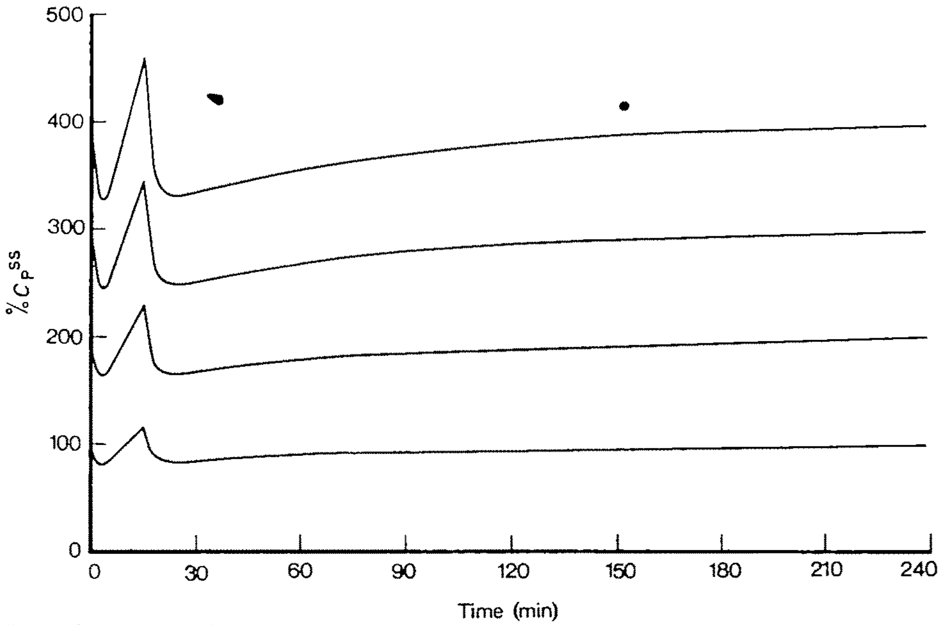

FIG. 8. Computer-predicted plasma concentration–time relationships for morphine to achieve C_P^{ss} = 400, 300, 200, and 100 ng ml^{-1} ±20%. Predictions based on data of Berkowitz and others (1975). See text for further details.

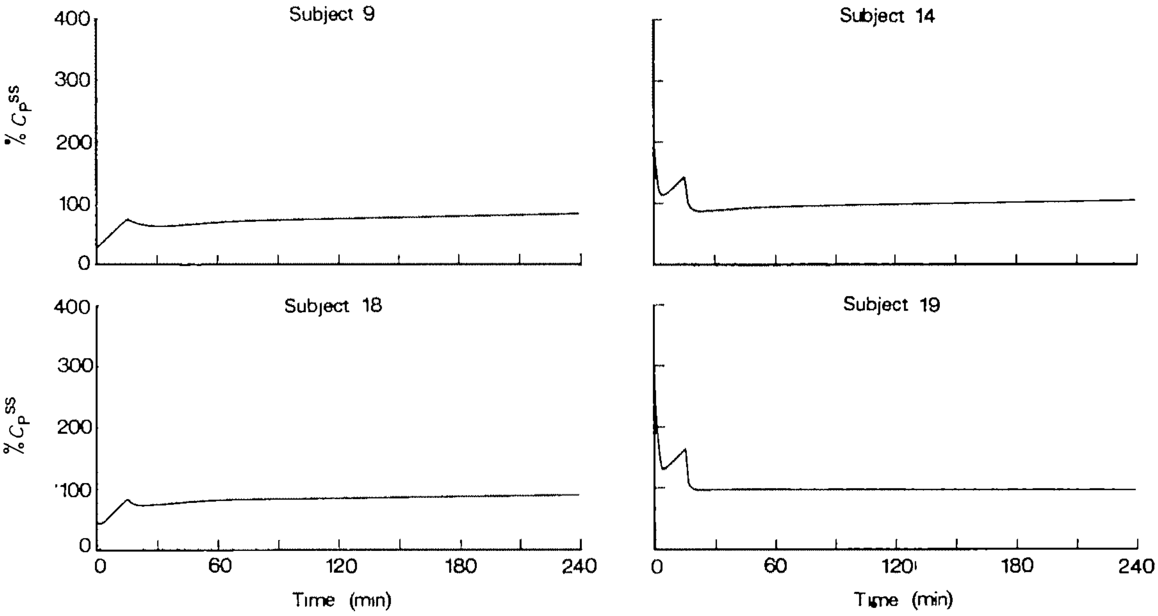

FIG. 9. Computer-predicted plasma concentration–time relationships for individual subjects of Berkowitz and others (1975). The infusion regimen was determined from the pooled data of Berkowitz and others (1975). Deviation from predicted is a measure of the extent of the error which can be expected from using *pooled* data to predict *individual* steady-state plasma morphine concentrations.

The original parameters for the pooled and individual data of Berkowitz and others (1975) are given in table I. An estimate of the probable range of responses in individual subjects is given by computer simulations of predicted steady-state plasma morphine concentrations in some of Berkowitz and others' subjects given the above regimen. These simulations are shown in figure 9. They were chosen from the most "outlying" of Berkowitz and colleagues' subjects (table I). Thus, the estimates of C_p shown in figure 9 represent the probable worst cases of deviation from target C_p^{ss} as a result of the error inherent in using pooled data to predict individual responses. In all cases an approximate steady state is present by 30 min, and initial plasma concentrations range from transient high of almost four times C_p^{ss} to an initial low concentration of 30%.

DISCUSSION

This paper describes a general method, modified from Vaughan and Tucker (1976), for obtaining rapidly and maintaining steady-state plasma concentrations of drugs given i.v. The mean data of Berkowitz and others (1975) for the disposition of morphine are used to calculate a regimen for i.v. morphine to maintain plasma concentration within 20% of the desired concentration after an initial bolus injection.

Although the mathematical analysis appears complicated, the practical application of the method is relatively straightforward using a computer. The computer-simulated curves described in this paper suggest that the method could improve precision of control of plasma drug concentration.

Some practical limitations of the method are suggested. First, if there is wide inter-individual variation in V_1 or k_{10}, an infusion regimen developed from averaged data will have limited precision when applied to individual patients. The extent of this limitation depends on the degree of inter-individual variation. Further experiments are required for different drugs to compare the precision of the method for individual and group predictions. It is likely that, for most drugs, there will be greater inter-individual variation of k_{10} than of V_1, a consequence of the many physiological factors contributing to inter-individual variation in drug disposition. Second, another potential source of error may occur in the estimation of $A+B$, required to estimate V_1; individual studies of different drugs are needed, with rigorous attention to the timing of frequent blood samples, during the distribution phase, to quantitate this error and the physiological factors that influence it.

A further possible limiting factor in the application of the method is the extent to which the behaviour of a drug in the body deviates from the assumptions of the pharmacokinetic model. The model assumes that mixing of the drug in the central compartment is instantaneous and complete. For most drugs the central compartment volume represents approximately the circulation volume and a component of the extracellular fluid volume of organs with a very high blood flow (heart, brain, kidney and liver). Mixing is probably very rapid in this compartment, but it is not instantaneous. Thus, during the 2–3 min following an i.v. bolus, a plasma sample from either venous or arterial blood may not precisely reflect "mean" central compartment concentration (C_1). If mixing is incomplete, plasma samples will, in most cases, underestimate C_1. This difficulty is compounded by another problem: the rapidly injected bolus might cause an acute toxic effect on the myocardium as a result of the sudden exposure of the heart to a brief period of extremely high drug concentration as the venous "slug" is returned to the right side of the heart (Goldstein, Aronow and Kalman, 1968). These problems may introduce further errors in estimating V_1. They may be minimized by giving the bolus as a brief infusion to allow for near complete mixing before sampling blood for drug analysis. The determination of the pharmacokinetic disposition parameters when the initial bolus is administered as a brief infusion, requires the correction described by Loo and Riegelman (1970).

The data of Berkowitz and others (1975) were obtained from surgery patients known not to have intercurrent medical disorders. However, many different medical disorders can affect drug disposition and elimination; the extent to which such disorders prevent effective application of this approach remains to be determined.

The general utility of the technique depends on how closely biological effect is correlated with blood concentration of drug in a steady state. This is largely unknown for most i.v. drugs and also requires experimental testing. Given the assumption that biological effect does closely parallel blood and tissue concentration in the steady state, the technique has the advantage of providing rapid onset and smooth maintenance of effect and minimum toxicity. This would seem to be a desirable objective for the use of all drugs given i.v.

Pharmacokinetic analyses of the uptake and distribution characteristics of inhaled anaesthetics, and clinical experience, suggest that steady-state plasma concentration of these drugs provides steady anaesthesia effect. *A priori*, it is reasonable to expect that this also would hold true for drugs given parenterally. That such simple relationships need not exist in the unsteady or transient state was shown by Finck and others (1977), who studied morphine disposition in blood and brain following i.v. injection in the dog. These authors showed that $T_{\frac{1}{2}}$ of brain morphine was 4.1 h in contrast to $T_{\frac{1}{2}}$ for serum morphine of 1 h. They interpreted their results by suggesting that, once morphine enters the brain, the greater proportion of the drug was converted to the protonated form, thus providing less free base available to cross the blood–brain barrier and return to the circulation. This observation suggests that, after a bolus, a concentration gradient may exist between brain and plasma and that biological effect may be greater than expected and more prolonged than plasma concentrations would suggest. However, if steady-state morphine concentration is achieved in plasma, it is reasonable to predict that a steady morphine concentration will be achieved in the brain also within 20–30 min, and that this would be associated with a steady central pharmacological effect. Finck and others (1977) also showed the importance of $P\text{CO}_2$ as a determinant of serum and brain morphine disposition. During hypercarbia, they showed a 40% decrease in V_1 and a corresponding increase in plasma morphine concentration. It is not known whether this is a general effect of $P\text{CO}_2$ on drug distribution, an effect mediated via the influence of carbon dioxide on the cerebral circulation and cardiac output, a specific effect on the morphine molecule, or a combination of these. In a subsequent study these investigators showed that hypocarbia also led to increased plasma morphine concentrations; clearly, different mechanisms were operative in this situation (Nishateno et al., 1979). Both studies indicate that, in studies of constant plasma concentration kinetics, it is important to control acid–base variables.

The potential of this theoretical approach to obtain steady-state drug concentration and effect justifies further study in healthy subjects and with computer simulation techniques, using drugs such as the muscle relaxants, narcotics and barbiturates in which both drug concentration and drug effect can be measured precisely.

APPENDIX

GLOSSARY OF ABBREVIATIONS

V_1 = apparent volume of the central compartment
V_2 = apparent volume of the peripheral compartment
V^{β} = apparent volume of distribution of drug in post-distributive phase
C_1 = concentration of drug in the central compartment
C_2 = concentration of drug in the peripheral compartment
C_p = concentration of drug in the plasma
C_p^{ss} = concentration in the plasma at steady state
C_{pe} = concentration in the plasma as a result of the exponential infusion, Qe
C_{br} = mean concentration of drug in brain tissue
C_1^{0} = mean concentration of drug in the central compartment at $t = 0$
C_1^{eq} = mean concentration of drug in the central compartment at equilibrium
t = time after i.v. injection
k_{12} = first order rate constant for drug transfer from the first to the second compartment
k_{21} = first order rate constant for drug transfer from the second to the first compartment
k_{10} = first order rate constant for drug elimination from the central compartment
$A, B,$
α, β = hybrid constants, each a complex function of the parameters of the model
$X\mathrm{d}$ = i.v. loading dose, given at time $t = 0$
e = exponential constant
$Q\mathrm{e}$ = exponentially decreasing infusion rate of Vaughan and Tucker's (1976) method
$Q_1\mathrm{e}$ = a component of the drug infusion rate from 0 to 15 min
Q^{ss} = steady state drug infusion rate from 15 min to infinity
Q_1 = drug infusion rate from 0 to 15 min ($Q_1\mathrm{e} + Q^{ss}$)
F, G = symbols used for complex functions of model parameters in the equation derived as a general expression for C_p when a loading dose is combined with a constant-rate infusion
U_1 = a constant derived from model parameters, and used by Vaughan and Tucker to compute an exponential infusion rate
t_1 = Time duration of first constant rate infusion, in relation to time of administration of bolus dose
$T_{\frac{1}{2}}$ = half-life (time for halving of drug concentration)

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NOTE: The program listing for the program to compute infusion regimens from pharmacokinetic constants (VANDT) is available from the corresponding author.

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METHODE PERMETTANT D'ATTEINDRE RAPIDEMENT UN EQUILIBRE CINETIQUE DES CONCENTRATIONS DE MEDICAMENTS ADMINISTRES PAR VOIE INTRAVEINEUSE

RESUME

Nous décrivons dans cet article la base théorique d'une méthode pharmacocinétique permettant d'obtenir rapidement et de maintenir dans le plasma une concentration constante du médicament administré par voie intraveineuse. Nous donnons comme exemples des doses de régimes d'équilibre cinétique des simulations par ordinateur de la disposition de la morphine chez l'homme, en nous basant sur des constantes pharmacocinétiques obtenues dans les livres. L'utilité et les limites éventuelles de cette méthode sont largement débattues.

EINE METHODE ZUR SCHNELLEN HERSTELLUNG VON STATIONÄREN BLUTKONZENTRATIONEN VON INTRAVENÖS VERABREICHTEN DROGEN

ZUSAMMENFASSUNG

Die theoretische Basis einer pharmakokinetischen Methode zur schnellen Herstellung und Aufrechterhaltung einer stationären Plasmakonzentration einer intravenös verabreichten Droge wird beschrieben. Computer-Simulationen von der Morphiumdisposition beim Menschen, auf der Basis von aus der Literatur entnommenen Konstanten, werden als Beispiele von stationären Dosisprogrammen angegeben. Die Nützlichkeit und die möglichen Grenzen der Methode werden diskutiert.

METODO PARA LOGRAR RAPIDAMENTE CONCENTRACIONES DE ESTADO DE REGIMEN DE DROGAS ADMINISTRADAS INTRAVENOSAMENTE

SUMARIO

Se describe la base teórica de un método farmacocinético para obtener rápidamente y para mantener una concentración constante en el plasma de una droga administrada intravenosamente. Se proveen simulaciones mediante ordenador de la disposición de la morfina en el hombre, haciendo uso de constantes farmacocinéticas obtenidas de la literatura existente, a guisa de ejemplos de las condiciones de dosis en el estado de régimen. Se discuten la utilidad y las limitaciones potenciales del método.

Br. J. Anaesth. (1980), 53, 1259

CONTROLLED-RELEASE MORPHINE TABLETS

A double-blind trial in dental surgery patients

G. W. Hanks, N. M. Rose, G. W. Aherne, E. M. Piall, S. Fairfield and T. Trueman

SUMMARY

We report a randomized double-blind comparison of controlled-release morphine tablets (MST-1; 2 × 10 mg) and oral morphine sulphate in solution (20 mg) in 28 patients (20 females) who had undergone removal of impacted lower third molars or a dental clearance under general anaesthetic. The response in both groups was very poor: eight of 15 patients in MST-1 group and six of 13 patients in the standard group required "rescue" analgesics and were withdrawn from the study within the first 2 h. No threshold plasma concentration of morphine corresponding to a particular analgesic effect was apparent. MST-1 produced significantly greater plasma concentrations at 8 h compared with the standard preparation. Controlled-release morphine, or any oral formulation of morphine, may not be suitable for the treatment of acute pain after operation.

MST-1 (Napp Laboratories) is a controlled-release tablet formulation of morphine sulphate 10 mg which, it is suggested, has a 12-h duration of action (Leslie, Rhodes and Black, 1980). However, there are as yet no clinical data on the duration of its analgesic effect. The pharmaceutical formulation (the "Continus" tablet) has been used for other drugs. It is known to be an effective sustained-release vehicle and to maintain blood concentrations over a prolonged period of time (Boroda et al., 1973).

Since MST-1 is very likely to be used in the period after operation, we have investigated its duration of analgesia and the plasma morphine concentrations after its use in patients who have undergone dental surgery. This is a model which has been increasingly used for the evaluation of oral analgesics (Cooper and Beaver, 1976; von Graffenried et al., 1980) since it has been shown to be reliable and has the advantage of being applicable to outpatients. We have completed a randomized double-blind evaluation of MST-1 in comparison with oral morphine sulphate in aqueous solution. This has been reported previously in outline (Hanks et al., 1981).

PATIENTS AND METHODS

Twenty-nine consecutive patients (21 female) admitted for removal of impacted lower third molars or dental clearance under general anaesthesia entered this study. They were aged between 18 and 65 yr. On admission they were given a detailed explanation of the purpose of the study and the procedures involved before consent was obtained.

On the morning of operation all patients received diazepam 7.5–20 mg orally (according to weight and build) 2 h before surgery. Anaesthesia was induced with thiopentone (maximum 500 mg i.v.); gallamine 20 mg i.v. and suxamethonium (maximum) 100 mg i.v. were also given. After nasotracheal intubation and insertion of a throat pack, anaesthesia was maintained with nitrous oxide in oxygen and halothane with spontaneous breathing. A venous cannula was inserted to a convenient forearm vein during the operation and was kept patent with heparinized saline 10 u. ml^{-1}.

Patients were seen in the recovery room by a nurse observer. When conscious they were asked if they had pain and if they complained of moderate or severe pain they were admitted to the study. Baseline assessments were carried out and a 10-ml venous blood sample was obtained. Patients were randomly allocated to treatment with either MST-1 (2 × 10 mg tablets) or a standard solution of morphine sulphate 20 mg in chloroform water

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made up to 4 ml. A double-dummy technique was used so that all patients received two tablets (either active or placebo) and 4 ml of solution (either active or placebo). Patients were subsequently interviewed by the same nurse observer at 30 min, 1, 2, 4 and 8 h following administration of the analgesic. Pain intensity at baseline and at each subsequent interview was based on the patient's own assessment and scored on a four-point scale: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain. Pain intensity difference (PID) scores were derived by calculating the arithmetical difference between a patient's pre-treatment pain intensity score and each post-treatment score. An SPID (Sum of Pain Intensity Difference) score was then calculated for each patient. Patients were also asked to complete a 10-cm line visual analogue scale marked at one end with the words "No pain" (0 mm) and at the other end "Worst Possible Pain" (100 mm).

At each interview after treatment patients were asked to give an estimate of pain relief on a scale from 0 to 4: 0 = none; 1 = slight; 2 = moderate; 3 = extensive; 4 = complete. A visual analogue scale marked at one end "Complete Pain Relief" (0 mm) and at the other "No Pain Relief" (100 mm) was completed at the same time. Any ill-effects experienced by the patient were noted and a venous blood sample was taken. If patients experienced no pain relief and asked for additional analgesics they were given two Distalgesic (dextropropoxyphene plus paracetamol) tablets. Patients who received the "rescue" analgesic were withdrawn from further assessment and for the purpose of analysis their baseline pain intensity score was substituted for any interview not completed.

Plasma morphine concentrations were measured by radioimmunoassay (Aherne et al., 1976). The antiserum used was raised in a goat to 6-succinyl morphine-BSA and cross-reacted with morphine 3-glucuronide by less than 10%. For this reason plasma morphine was measured as cross-reacting morphine or "morphine equivalents".

RESULTS

Of the 29 patients who entered the study one was excluded because her initial pain severity was "mild". There were no important differences between the two groups in terms of age and sex distribution (MST-1: 10 females of mean age 27.6 yr, five males of mean age 25.6 yr; standard morphine sulphate: 10 females of mean age 22.9 yr, three males of mean age 28 yr) and the type of operation (removal of impacted lower third molars in almost all cases).

The study was discontinued earlier than planned because response was extremely poor. Eight of 15 of the MST-1 patients and six of 13 of the standard morphine sulphate patients required rescue analgesics because they had failed to experience any change in pain intensity within the first 2 h after administration of morphine.

Table I shows the ordinal pain intensity difference (PID) and the sum of pain intensity difference (SPID) scores and pain relief scores. The corresponding visual analogue scale (VAS) scores followed very similar patterns. Statistical analysis (using the Mann-Whitney *U*-test for the ordinal scale and Student's *t* test for the VAS) revealed a significant difference in favour of the standard solution at 1 h (PID ordinal) and at 2 h (pain relief VAS), although the scores favoured the standard morphine group throughout.

Only four patients experienced unequivocally good pain-relief: one in the MST-1 group and three in the standard morphine group.

Plasma morphine concentrations

The results of the plasma morphine analyses and the plasma concentration–time curves for the two preparations are shown in table II and figure 1.

TABLE I. *Pain intensity difference (PID), sum of pain intensity difference (SPID) scores and pain relief scores (mean ± SEM).**P < 0.05 *(Mann–Whitney* U *test)*

	0.5 h	1 h	2 h	4 h	8 h	SPID
Standard morphine sulphate						
PID	0.58±0.15	0.88±0.11*	1.12±0.18	0.67±0.23	1.00±0.32	3.96±0.7
Pain relief	1.46±0.27	1.88±0.25	2.12±0.3	1.96±0.33	2.50±0.39	
MST-1						
PID	0.25±0.11	0.43±0.13*	0.43±0.2	0.67±0.21	0.67±0.25	2.40±0.7
Pain relief	1.04±0.17	1.27±0.21	1.29±0.3	1.80±0.31	1.87±0.34	

TABLE II. *Plasma morphine concentrations (mean ± SEM) ("morphine equivalents"). *$P < 0.05$; C_{max} = peak plasma concentrations; T_{max} = time to peak plasma concentration; AUC (8 h) = cumulative area under plasma concentration–time curve for 8-h period (trapezoidal method)*

	C_{max} (ng ml^{-1})	T_{max} (h)	Mean concentration (ng ml^{-1}) at 0.5 h	1 h	2 h	4 h	8 h	AUC (8 h) (ng h ml^{-1})
Standard morphine sulphate ($n = 8$)	73.1 ± 12.8	2.9 ± 0.4	14.0 ± 9.9	31.3 ± 15.4	56.5 ± 12.7	49.1 ± 6.1	14.0 ± 2.2*	290.4 ± 33.7
MST-1 ($n = 12$)	55.0 ± 14.8	3.3 ± 0.5	5.7 ± 3.6	14.9 ± 5.3	39.3 ± 7.2	47.2 ± 5.5	24.0 ± 3.3*	250.9 ± 25.7

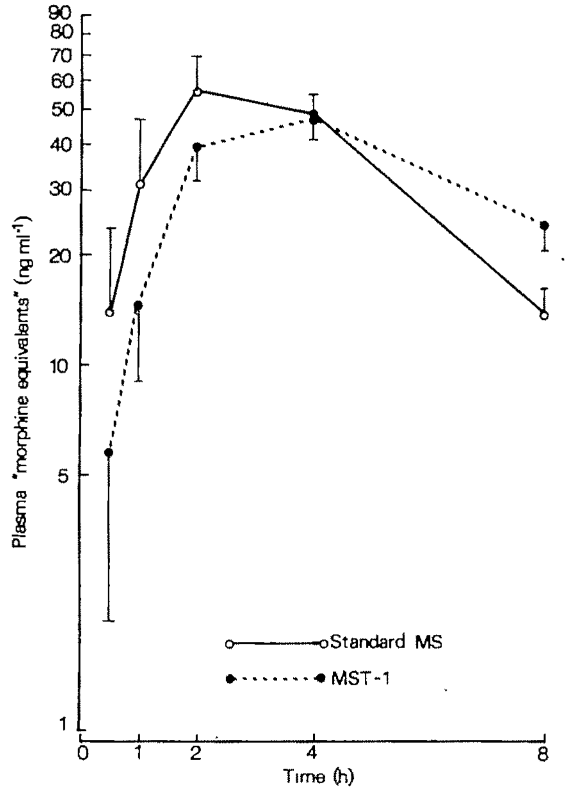

FIG. 1. Mean plasma concentrations of "morphine equivalents" (± SEM).

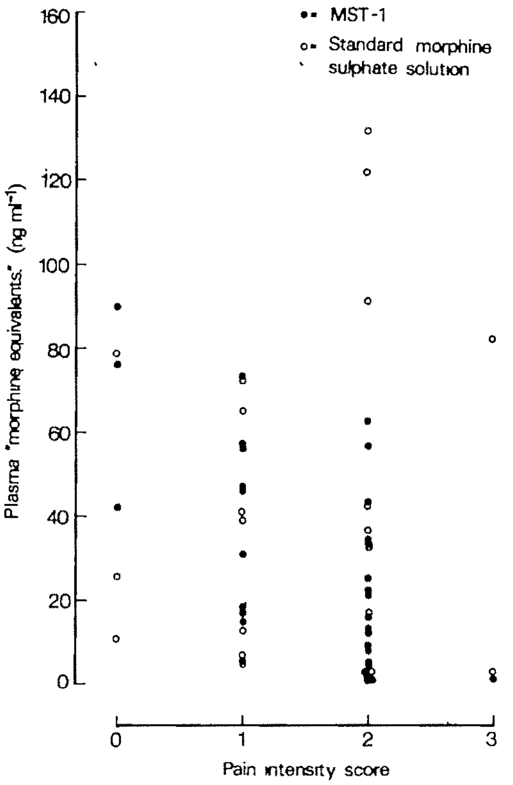

FIG. 2. Individual plasma concentrations of "morphine equivalents" corresponding to ordinal pain intensity scores.

The only statistically significant difference was at 8 h.

Figure 2 shows the distribution of morphine plasma concentrations at each point on the ordinal pain intensity scale, and figure 3 the plasma concentrations plotted against visual analogue scale pain intensity scores. When examined separately there was a good negative correlation between the MST-1 plasma concentrations and pain intensity ($r = -0.62$, $P < 0.001$ on the ordinal scale; $r = -0.4$, $P < 0.05$ on the visual analogue scale), but no such relationship between the standard morphine sulphate plasma concentrations and pain intensity ($r = 0.03$ and $r = 0.15$ respectively). These results were supported by an examination of the ordinal pain relief scale for MST-1, where there was a positive correlation with plasma morphine concentration ($r = 0.57$, $P < 0.001$), but again no correlation for the standard morphine solution. It is noteworthy that

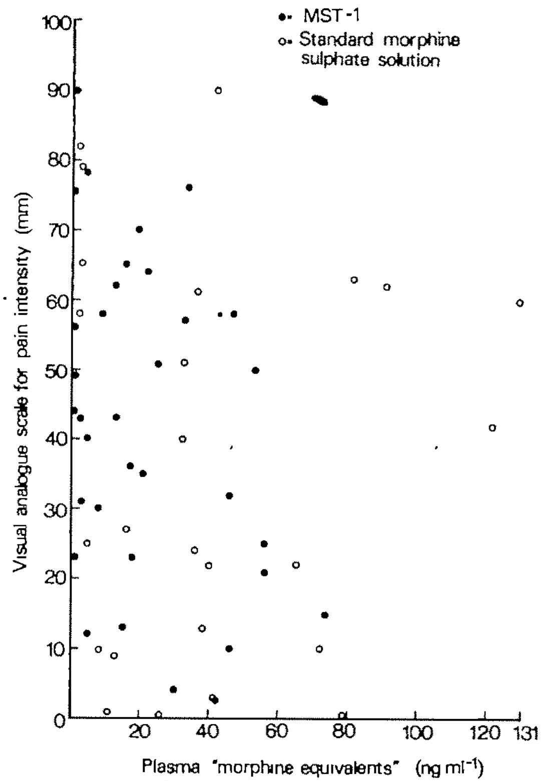

FIG. 3. Individual plasma concentrations of "morphine equivalents" corresponding to visual analogue scale pain intensity scores.

the two patients with the highest peak concentrations (122 ng ml^{-1} and 131 ng ml^{-1}, both in the standard morphine sulphate group and both at 2 h) required rescue analgesics because of unremitting severe pain.

Adverse effects

Both preparations were generally well tolerated. Drowsiness, transient nausea and dizziness were reported equally in both groups. In only one patient (who had received MST-1) were symptoms of nausea severe, but this patient had a history of nausea and vomiting following any general anaesthetic.

DISCUSSION

From our results it is clear that oral morphine in either formulation is not suitable for the treatment of pain after dental surgery. The poor analgesic effect of *single doses* of orally administered morphine was demonstrated a long time ago (Beecher et al., 1953) and has been the basis for suggesting that the oral to parenteral potency of morphine is in the region of 1 : 6 or 1 : 8 (Houde, Wallenstein and Beaver, 1965). Our results are in accord with this view, although we were surprised at how ineffective both preparations were. We had selected a dose (20 mg) which we felt would be effective, but it was clearly inadequate.

It has been widely taught that morphine is ineffective when given by mouth, but there is extensive clinical experience with oral morphine in the treatment of terminal cancer pain where it has become the strong narcotic of choice (Editorial, 1980). In this situation the potency ratio of oral to parenteral morphine is approximately 1 : 3 (Twycross, 1980). The difference in apparent potency in acute and chronic use has its basis in differences in the pharmacokinetics of single and repeated doses of oral morphine. Morphine undergoes extensive "first pass" metabolism to (inactive) morphine-3-glucuronide both in the intestinal mucosa and in the liver. There is some evidence that this glucuronidation of morphine is dose-dependent; total morphine clearance has been shown to be dose related (Garrett and Jackson, 1979). The enterohepatic recirculation of morphine which has been demonstrated in animals (Walsh and Levine, 1975; Dahlstrom and Paalzow, 1978) probably also occurs in man and might produce a secondary peak of unconjugated morphine which, on chronic dosing, might be expected to contribute significantly to circulating concentrations.

Some authors have suggested that there is a relationship between plasma concentrations of unconjugated morphine and analgesic effects (Berkowitz et al., 1975; Dahlstrom et al., 1979) with a threshold concentration of 50 ng ml^{-1} being necessary for relief of moderate to severe pain. However no relationship between the plasma concentration of morphine and morphine-induced changes in ventilatory function was found by Rigg (1978).

We have shown a difference between the standard morphine solution and the controlled-release preparation. The latter produced plasma concentrations which showed an apparently good correlation with pain intensity (on both scales) and pain relief. However, the analgesic response was so poor that it is difficult to interpret this result and it may be that the correlation is spurious. Plasma concentrations following the standard solution did not appear to bear any relationship to pain intensity measures and in neither case was there any suggestion of a threshold analgesic plasma concentration of unconjugated morphine.

Our results indicate that MST-1 administration does produce sustained plasma concentrations of morphine which may be adequate after chronic administration only, but further clinical and pharmacokinetic data after repeated dosage are required.

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COMPRIMES DE MORPHINE A DISPERSION CONTROLEE

Essais à double inconnue effectués sur des patients subissant une opération de chirurgie dentaire

RESUME

Notre rapport couvre une comparaison à double inconnue, faite au hasard, sur des cachets de morphine à dispersion contrôlée (MST-1; 2 × 10 mg) et sur le sulfate de morphine en solution (20 mg) administrée par voie buccale à 28 patients (dont 20 femmes) ayant subi une extraction de la troisième molaire inférieure (barrée) ou une extraction dentaire totale sous anesthésie générale. La réaction a été médiocre dans les deux groupes: huit patients sur les 15 du groupe MST-1 et six patients sur les 13 du groupe standard ont dû recevoir des analgésiques de "secours" et être retirés de l'étude au cours des deux premières heures. On n'a constaté aucune concentration de seuil de morphine dans le plasma, correspondant à effet analgésique particulier. MST-1 a produit après 8 h des concentrations dans le plasma sensiblement plus fortes qu'avec la préparation standard. La morphine à dispersion contrôlée ou toute autre formulation de morphine pour administration par voie buccale peut ne pas convenir pour le traitement des douleurs aiguës survenant après les interventions chirurgicales.

MORPHIUMTABLETTEN MIT GESTEUERTER FREISETZUNG:

Doppelblind-Versuch bei Patienten einer zahnärztlichen Klinik

ZUSAMMENFASSUNG

Wir berichten über einen wahllosen Doppelblind-Vergleich zwischen Morphiumtabletten mit gesteuerter Freisetzung (MST-1; 2 × 10 mg) und oral verabreichtem Morphiumsulfat in einer Lösung (20 mg) bei 28 Patienten (20 davon weiblichen Geschlechts), die sich der Extraktion eines retinierten dritten Molars oder einer vollständigen Räumung unter Allgemeinnarkose unterzogen hatten. Bei beiden Gruppen war die Reaktion sehr schlecht; 8 von den 15 Patienten der MST-1 Gruppe und 6 von den 13 Patienten bei der Standardgruppe mussten mit Schmerzlinderungsmitteln "gerettet" werden und sind schon innerhalb der ersten 2 Stunden aus dem Versuch ausgeschieden. Dabei wurde keine Grenzplasmakonzentration von Morphium festgestellt, die einer spezifischen analgesischen Wirkung entsprach. MST-1 führte zu bedeutend grösseren Plasmakonzentrationen nach 8 Stunden, verglichen mit dem Standardpräparat. Morphium mit gesteuerter Freisetzung, oder irgend eine orale Formulierung von Morphium, könnte sich als ungeeignet für die Behandlung von akuten Schmerzen nach der Operation erweisen.

TABLETAS DE MORFINA DE DESCARGA CONTROLADA

Prueba de doble anonimato en pacientes sometidos a cirujía dental

SUMARIO

Se efectuó una comparación aleatoria de doble anonimato de tabletas de morfina de descarga controlada (MST-1; 2 × 10 mg) y sulfato de morfina por vía bucal (20 mg) en 28 pacientes (20 mujeres) quienes habían sido sometidos a la extraccion de molares terceras inferiores chocados, o a una eliminación dental bajo anestesia general. La respuesta en ambos grupos fue muy pobre: 8 de los 15 pacientes del grupo de MST-1 y 6 de los 13 pacientes en el grupo normal, necesitaron analgesicos de "urgencia" y fueron retirados del estudio a las 2 h. No fueron aparentes las concentraciones umbrales de morfina en el plasma, correspondientes a un efecto analgésico particular. El MST-1 produjo concentraciones en el plasma que fueron significativamente superiores al cambo de las 8 h, en comparación con la preparación normal. La morfina de descarga controlada, o cualquier otra formulación de morfina, puede no ser adecuada para el tratamiento del dolor agudo posoperativo.

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REDUCTION OF VENOUS SEQUELAE OF I.V. DIAZEPAM WITH A FAT EMULSION AS SOLVENT

M. A. K. MATTILA, M.-L. ROSSI, M. K. RUOPPI, M. KORHONEN, H. M. LARNI AND S. KORTELAINEN

SUMMARY

Venous sequelae were studied in 93 female patients undergoing minor gynaecological procedures. They were premedicated with diazepam i.v. dissolved in a fat emulsion (Diazemuls) injected to a superficial vein of the right hand. The patients observed the site of injection for 14 days and recorded their findings. Twenty-eight per cent reported mild tenderness and 7.5% mild or moderate swelling of short duration. Signs of thrombophlebitis were found in 2.2%. Thrombophlebitis after injection can be prevented effectively and safely using fat emulsion as a solvent for diazepam.

I.v. diazepam has been used widely as an adjuvant to general and local anaesthesia. It has good amnesic and myoneural blocking properties and a favourable interaction with many anaesthetics (Dundee and Haslett, 1970; Mattila, Rajpar and Pystynen, 1974; Mattila, Larni et al., 1979; Mattila, Säilä et al., 1979). Its effects on circulation and respiration are small and its therapeutic range is wide.

Increasing attention has been paid recently to thrombophlebitis following diazepam injection i.v. (Hegarty and Dundee, 1977; Mattila, Ruoppi et al., 1979; Korttila and Aromaa, 1980). Typically, this complication appears within a few days after injection as a local tender induration of the injected vein with oedema and redness. These symptoms are not severe but they may constrain everyday activities of patients since they cause pain and restriction of normal movements.

The pain following diazepam is associated with its water-insolubility. The most widely used solvent for diazepam is propylene glycol. When diazepam in propylene glycol is diluted with saline or becomes diluted by plasma after injection i.v. precipitation occurs which may cause irritation of the vein endothelium and result in thrombophlebitis (Jusko, Gretch and Gassett, 1973).

Earlier we reported (Mattila, Ruoppi et al., 1979) a significant reduction of thrombophlebitis by using Cremophor as a solvent instead of propylene glycol. However, the danger of anaphylactic reactions with Cremophor markedly reduces its clinical value (Clarke et al., 1975; Dundee, 1976).

Von Dardell, Mebius and Mossberg (1976) used fractionated soya-bean oil as a solvent for diazepam and found a frequency of 1.1% for post-injection thrombophlebitis. The mean duration of observation in their investigation was 8.7 days.

We have investigated the use of different solvents in earlier studies (Mattila, Ruoppi et al., 1979) to find a safe solution. This study was undertaken to investigate the reportedly reduced frequency of thrombophlebitis after injection with a diazepam formulation dissolved in soya-bean oil and emulsified in water (Diazemuls, Kabi-Vitrum).

PATIENTS AND METHODS

Diazepam 10 mg i.v. was used as premedication for 123 female patients undergoing minor gynaecological procedures (therapeutic abortion or diagnostic curettage), mean age 34.7 yr, range 16–82 yr. Informed consent was obtained from the patients. Diazepam was injected to a superficial vein of the right hand through a 22-gauge needle by one of the anaesthetists (M.A.K.M. or M.K.R.). After injection, the needle was removed and pressure was applied to the site for a few minutes. The patients received a short i.v. anaesthetic with atropine, flunitrazepam (Rohypnol), methohexitone (Brietal sodium) and fentanyl (Sublimaze), administered to the dorsal

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vein of the left hand through a 1.6 mm cannula (Intranule, Vygon).

When fully recovered from anaesthesia, the patients were requested by an anaesthetic nurse to observe the site of injection for 14 days and complete a questionnaire. They were asked to contact one of the anaesthetists if symptoms were severe.

The questionnaire included the following questions on the condition of the injection site on the dorsum of the right hand: swelling, redness and tenderness. These signs and symptoms were allocated to four grades; none, mild, moderate and severe. The patients were asked if movement of the hand and its use in everyday activities were restricted. In addition, they were asked to describe any vein symptoms in the left hand (where all other drugs were given) and for their comments on the anaesthetic.

RESULTS

Questionnaires were returned by 75.6% (93/123) of the patients. Results presented are from those 93. None contacted the anaesthetist concerning symptoms at the injection site. The frequency of symptoms occurring within 14 days after injection of diazepam i.v. is shown in table I. Table II gives the duration of swelling, redness and tenderness. The time of onset of the symptoms is shown in table III

The frequency of true thrombophlebitis which fulfilled the criteria of onset time and duration was 2.2% in patients (2/93) returning the questionnaire. The frequency of symptoms at the injection site of the left hand was 60% and 19.4% (18/93) were classified as true thrombophlebitis.

TABLE I. *Frequency (%) of venous symptoms after i.v. diazepam in a fat emulsion*

	Swelling	Redness	Tenderness	Disturbance of function	Disturbance of function affecting every-day activities
Mild	6.5	6.5	28.0	4.3	2.2
Moderate	1.0	1.0	0	0	0
Severe	0	0	0	0	0

TABLE II. *Duration of venous symptoms (days) after i.v. diazepam in a fat emulsion. Total number of patients with symptoms = 26*

	Duration (days)		
	1–3	4–7	8+
Swelling ($n=7$)	5	2	0
Redness ($n=7$)	4	3	0
Tenderness ($n=26$)	21	3	2

TABLE III. *Onset of symptoms (days) after injection of diazepam in a fat emulsion. Total number of patients = 26*

	Symptom		
Days after injection	Tenderness	Redness	Swelling
0	10	3	1
1	6	2	3
2	6	1	2
3	2	—	—
4	1	—	1
5	—	—	—
6	—	—	—
7	1	1	—
Total	26	7	7

DISCUSSION

As the venous sequelae were superficial, easily observed and primarily subjective, patients completed their own questionnaires. The large number of positive observations on the left hand shows, in our opinion, that the patients were prepared to record their signs and symptoms. Nevertheless, we do not wish to draw conclusions on the basis of the results of the left hand as several substances were injected into it which could have caused thrombophlebitis. Furthermore, the high percentage (75.6) of returned questionnaires reflected the patients' motivation.

Spontaneous complaints from patients are quite frequent when using other i.v. diazepam formulations but none was received in this study.

Classical signs and symptoms of thrombophlebitis appear first after a few days and reach a maximum 1–2 weeks after injection (Mattila, Ruoppi et al., 1979). The observation period was chosen as 14 days.

As shown in table II, tenderness lasted 1–3 days in 81% and 4–7 days in 11.5% of the patients with symptoms. The tenderness lasted long enough to be classified as thrombophlebitis in only two patients, but the symptoms were assessed as mild even though they disturbed everyday activities.

The diazepam injection was performed using an atraumatic technique (Lepoivre, Alderweireldt and Delaruelle, 1973) and the needle was removed immediately after injection. In spite of these precautions, the development of a local haematoma was possible and the immediate appearance of swelling, redness and tenderness also suggests this (table III). Only in one patient did tenderness start 1 week after injection and last long enough to suggest typical thrombophlebitis.

The true frequency of significant injection thrombophlebitis calculated on basis of the time of appearance and duration of symptoms and effect on everyday activities was 2.2% (2/93) in this series. This corresponds well with the frequency of 1.1% reported by von Dardel, Mebius and Mossberg (1976) and 4% by Olesen and Hüttel (1980).

The frequency of thrombophlebitis following diazepam in a fat emulsion was significantly less than that after diazepam in propylene glycol (21–62%) (Siebke, Ellertsen and Lind, 1976; Hegarty and Dundee, 1977; Mattila, Ruoppi et al., 1979; Korttila and Aromaa, 1980).

Using Cremophor as a solvent for diazepam significantly reduces the frequency of thrombophlebitis after injection. In the investigation by Mattila, Ruoppi and others (1979) it was 3.4% and in Olesen and Hüttel's (1980) study it was 9%. Nevertheless, the possibility of anaphylactic reactions (Clarke et al., 1975; Dundee, 1976) associated with Cremophor reduces its clinical value as a solvent for diazepam.

The differences in the frequency of thrombophlebitis between formulations of flunitrazepam (5%), lorazepam (15%) and diazepam (39%) (Hegarty and Dundee, 1977), show clearly that the primary cause of thrombophlebitis is precipitation of the benzodiazepines and not the solvent used (propylene glycol).

Patients often complain about pain and a burning sensation during injection of diazepam. In this study no patient complained of pain during injection. Olesen and Hüttel (1980) reported a sensation of burning in 78% of the patients injected with diazepam in propylene glycol compared with 1% for diazepam in fat emulsion.

Diazepam in fat emulsion provides a safe, practical solution to the problem of post-injection thrombophlebitis associated with other diazepam formulations. The large number (18/93, 19.4%) of venous sequelae which occurred in the vein where the other agents were given indicate that these also should be thoroughly investigated.

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REDUCTION DES SEQUELLES VEINEUSES RESULTANT DES INJECTIONS INTRAVEINEUSES DE DIAZEPAM A L'AIDE D'UNE EMULSION GRASSE AGISSANT EN TANT QUE SOLVANT

RESUME

On a étudié sur 93 patientes les séquelles veineuses après une intervention gynécologique mineure. Il leur a été administré une médication préopératoire par voie intraveineuse: diazépam dissout dans une émulsion grasse (Diazémuls), injecté dans une veine superficielle de la main droite. Les patientes ont observé l'emplacement de l'injection pendant 14 jours et pris note de leurs observations. Vingt-huit pour cent d'entre-elles ont signalé une légère sensibilité douloureuse à la pression et 7,5% une enflure légère ou modérée de courte durée. On a trouvé dans 2,2% des cas des signes de thrombophlébite. On peut éviter d'une manière efficace et sûre toute thrombophlébite après une injection en utilisant une émulsion grasse comme solvant pour la diazépam.

VERMINDERUNG DER VENÖSEN FOLGE-ERSCHEINUNGEN VON INTRAVENÖS VERABREICHTEM DIAZEPAM MIT EINEM FETTEMULSION ALS LÖSUNGSMITTEL

ZUSAMMENFASSUNG

Die venösen Folgeerscheinungen wurden bei 93 weiblichen Patienten studiert, die sich kleinen gynäkologischen Operationen unterzogen. Sie wurden mit intravenösem Diazepam vorbehandelt, das in einer Fettemulsion aufgelöst war (Diazemuls) und in eine oberflächliche Vene der rechten Hand injiziert wurde. Die Patienten beobachteten die Injektionsstelle über einen Zeitraum von 14 Tagen und notierten den Befund. Achtundzwanzig Prozent berichteten über eine leichte Empfindlichkeit und 7,5% berichteten über eine leichte oder mittlere Schwellung auf kurze Zeit. Bei 2,2% wurden Anzeichen von Thrombophlebitis gefunden. Wenn eine Fettemulsion als Lösungsmittel für Diazepam verwendet wird, kann Thrombophlebitis nach der Injektion leicht und sicher verhindert werden.

REDUCCION DE LA SECUELA VENOSA DEL DIAZEPAN INTRAVENOSO MEDIANTE UNA EMULSION DE GRASAS ACTUANDO COMO DISOLVENTE

SUMARIO

Se estudiaron las secuelas venosas en 93 mujeres sometidas a procedimientos ginecológicos menores. Se las premedicó con diazepan intravenoso disuelto en una solución de grasas (Diazemuls) inyectado en una vena superficial de la mano derecha. Las pacientes observaron el lugar de la inyección por espacio de 14 días y registraron los resultados. El 28% informaron de una suavidad de grado medio y el 7,5% de dolor suave o moderado. Se encontraron signos de tromboflebitis en el 2,2% de las pacientes. La tromboflebitis posterior a la inyección puede prevenirse efectivamente y con seguridad usando una emulsión de grasas como disolvente del diazepan.

Br. J. Anaesth. (1981), 53, 1269

DIAZEPAM IN RECTAL SOLUTION AS PREMEDICATION IN CHILDREN, WITH SPECIAL REFERENCE TO SERUM CONCENTRATIONS

M. A. K. MATTILA, M. K. RUOPPI, E. AHLSTRÖM-BENGS, H. M. LARNI AND P. O. PEKKOLA

SUMMARY

The absorption of rectal diazepam solution was studied in 22 children aged 1–9 yr by measuring serum concentrations. The mean dose was 0.27 ± 0.09 mg kg^{-1}. The mean serum concentration was 98.5 ± 53.5 ng ml^{-1} 4 min after administration and 206.7 ± 105.8 ng ml^{-1} at 11 min. The correlation between dose and serum concentration was statistically significant at both times. With a dose of 0.4–0.5 mg kg^{-1} an adequate serum concentration was achieved within 5–6 min. No side-effects were observed. A rectal solution provides a faster, more effective and reliable alternative to tablets and suppositories, and to the uncertain i.m. injection of diazepam. Meticulous nursing is important.

Sedative premedication is prescribed to decrease the anxiety of the patient before anaesthetic and operative procedures. Since the regimens of premedication are dominated by tradition originating in the ether period of anaesthesia, children are most often premedicated parenterally with an opiate and an anticholinergic agent. Children do not like injections and since the sedative effect may be inadequate, there may be technical difficulties for the anaesthetist and psychological stress to the patient.

Any compassionate advice given by the anaesthetist requires a pharmacological supplement to help alleviate the patient's anxiety (Johnstone, 1976). Benzodiazepines can be administered effectively to suppress emotional disturbances with the prerequisite that adequate concentrations are achieved in the serum and in the c.n.s. benzodiazepine receptors (Haffely, 1977). Thus it is important that the correct route of administration is used and an adequate dose given. Diazepam solution is rapidly and effectively absorbed by the rectal route (Agurell et al., 1975; Knudsen, 1977; Moolenaar et al., 1980). Children in hospital seem to accept this painless form of administration perhaps because they are acquainted with rectal temperature measurements. Five years practical experience with this technique have largely confirmed this, although there have been failures: in a clinical evaluation of 148 children the effect of rectal diazepam solution was estimated to be good in 53% (Mattila et al., 1980). The aim of the present study was to determine if adequate serum concentrations were achieved consistently and within a reasonable time following the rectal administration of a solution of diazepam.

PATIENTS AND METHODS

Twenty-two children aged 1–9 yr (mean 5.5 yr) and weighing 19.9 ± 5.2 kg, undergoing minor surgical operations under general anaesthesia were premedicated with diazepam 5 mg or 10 mg as rectal solution (Stesolid rectiol, Dumex A/S, Copenhagen). The rectal solution was supplied in disposable tubes of diazepam 5 and 10 mg in 2.5 ml. The child was placed on its side or prone (over a nurse's knees), the rectal tube inserted to the rectum and its contents emptied. The tube must be squeezed firmly while being removed and the buttocks compressed together.

Venous blood was sampled at 4 ± 1 min and 11 ± 1 min after administration of the drug and the concentration of diazepam in the serum estimated using the gas chromatographic method described by Arnold (1975).

Statistical methods

Linear regression analysis was used to assess the relationship between the dose of diazepam and the serum concentration. The dose (mg kg^{-1}) was taken as the independent variable X and the serum concentration of diazepam (ng kg^{-1}) as the functionally dependent variable Y. A straight-line linear model for the bivariate data was expressed as $Y = bX + k$, in which b is the slope and k the Y-

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intercept. The t-statistic was calculated using the formula $t+\sqrt{(n-2)}\,r^2/(1-r^2)$ in which n was the number of samples and r the correlation coefficient. Fisher and Yates' statistical tables were used in the determination of the values for P.

RESULTS

The serum concentrations of diazepam at 4 ± 1 min and 11 ± 1 min after administration of the rectal solution are shown in figure 1. The mean serum concentration was $98.5 \pm 53\,\text{ng ml}^{-1}$ at 4 ± 1 min and $206.6 \pm 105\,\text{ng ml}^{-1}$ at 11 ± 1 min. The serum concentration had exceeded the suggested sedative value of $150\,\text{ng ml}^{-1}$ in 18.8% of patients at 4 ± 1 min and in 68.2% at 11 ± 1 min. There were 10 patients (45.5%) with low concentrations of diazepam at 4 ± 1 min and 5 patients (22.7%) at 11 ± 1 min.

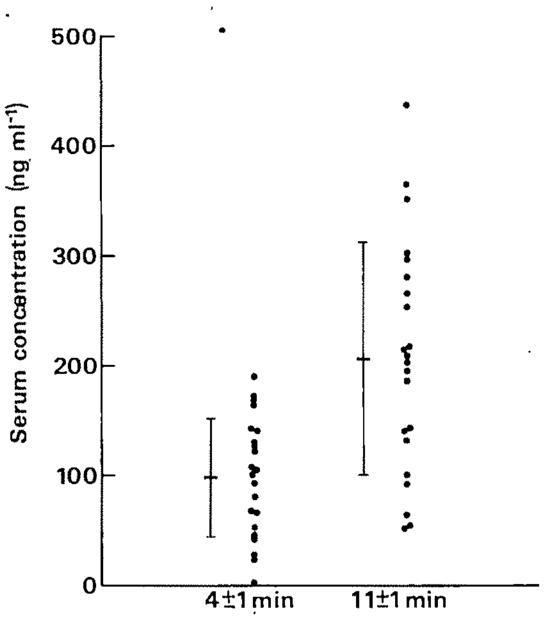

FIG. 1. Serum concentrations of diazepam at 4 ± 1 min and 11 ± 1 min after administration of diazepam as a rectal solution.

The mean dose of diazepam was $0.27 \pm 0.09\,\text{mg kg}^{-1}$. Figure 2 shows the relationship of serum concentration to the dose of diazepam at 4 ± 1 min after administration of the rectal solution, and figure 3 the corresponding correlation at 11 ± 1 min. The correlation was statistically significant ($P < 0.05$) at 4 ± 1 min and at 11 ± 1 min ($P < 0.001$). To reach a serum concentration of $150\,\text{ng ml}^{-1}$ at 4 ± 1 min, a dose of $0.463\,\text{mg kg}^{-1}$ was needed, and at 11 ± 1 min $0.141\,\text{mg kg}^{-1}$.

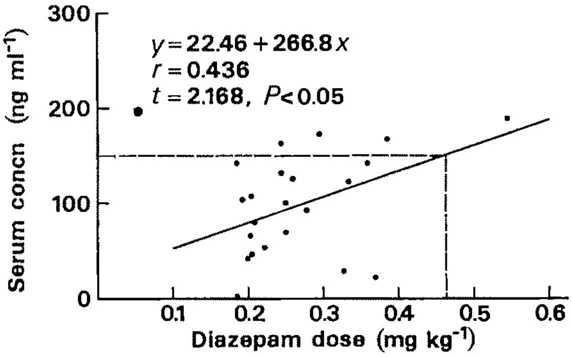

FIG. 2. Correlation between serum concentration (ng ml^{-1}) and the dose at 4 ± 1 min after administration of diazepam as a rectal solution.

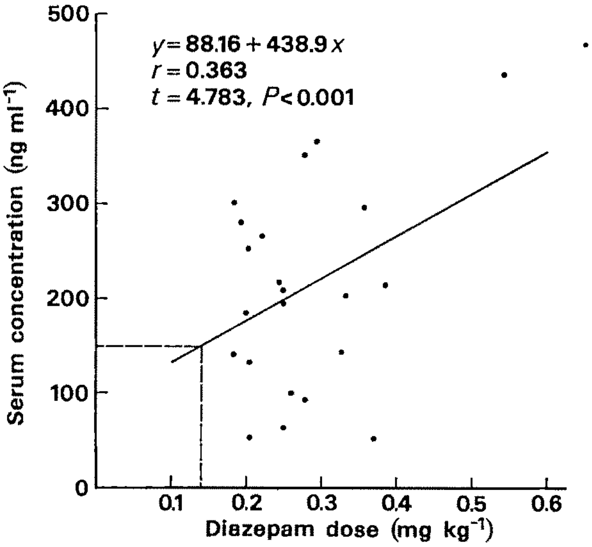

FIG. 3. Correlation between serum concentration (ng ml^{-1}) and the dose at 11 ± 1 min after administration of diazepam as a rectal solution.

DISCUSSION

The value of diazepam as a rectal solution in premedication is difficult to assess by subjective means alone. The degree of sedation is attributable not only to the effect of the diazepam, but also to such central factors as the behaviour, nature of the child and the influence of the parents. The age of the child is an important factor (Lindgren, Saarnivaara and Himberg, 1979); Doughty (1959) observed that improvement in behaviour was associated with increasing age in unsedated children. Moreover sedation and anxiolysis are not synonymous (Conner, 1978); anxiolysis is a subjective experience of the patient and sedation is equanimity noted by observers.

Benzodiazepines exert their effects in the brain (Haffely, 1977), where they have a selective effect on gamma-aminobutyric acid-mediated synaptic processes. Serum concentration and clinical effect do not always correlate (Moolenaar et al., 1980), because of differences in the basic activity of the limbic system.

The aim in measurement of serum concentration in this study was to control the absorption of diazepam as a rectal solution. Effective absorption is a prerequisite for clinical effect since it produces sufficient concentration of the drug in the serum and on the receptors. The absorption of diazepam solution through the rectal mucosa is rapid and effective. After a mean dose of $0.27 \pm 0.09\,\mathrm{mg\,kg^{-1}}$ of rectal diazepam the serum concentration was $98.5 \pm 53\,\mathrm{ng\,ml^{-1}}$ at 4 ± 1 min and $206.6 \pm 105\,\mathrm{ng\,ml^{-1}}$ at 11 ± 1 min. In practice this means, that serum concentrations adequate for sedation are achieved in less than 10 min. The correlation between dose and concentration is obvious. In this study a relatively low dose (mean $0.27\,\mathrm{mg\,kg^{-1}}$) was used, but with a dose of 0.4–$0.5\,\mathrm{mg\,kg^{-1}}$ an adequate concentration can be obtained within 5–6 min. Pharmacokinetically, the rectal solution of diazepam is comparable to an i.v. injection, with the exception of lower bioavailability. Magnussen and coworkers (1979) calculated that bioavailability was $50 \pm 17\%$, which differs significantly from the value of 100% reported by Moolenaar and colleagues (1980).

There were between-individual differences in the serum concentrations of diazepam despite the same dose per kilogram body weight. These differences are probably the result of the technique of administration. It is very important to keep the tube vertical or at a 45° angle while squeezing, because, in the horizontal position 27% of the contents are retained within the tube (Magnussen et al., 1979). There may also be leakage through the anus if the patient is not kept on the side or prone with the buttocks compressed together. Faecal contents may absorb part of the administered dose. In this study no attempt was made to evacuate the rectal contents before medication. All these factors emphasize the importance of careful nursing technique. Fortunately, if the effect is inadequate, the administration of rectal diazepam can be repeated easily and safely.

The distribution of diazepam into three compartments is very rapid and the decrease of serum concentration is steep. Clinically, the effect is markedly decreased within 1 h and disappears totally within 4–6 h (Lundgren, Ekman and Blombäck, 1978). In practice, it is important to use the short peak concentration period for the cannulation of a vein and the induction of general anaesthesia.

The effect of diazepam is more sedative than anxiolytic (Harder et al., 1976; Forrest, Brown and Brown, 1977). A beneficial feature is its intrinsic amnesic effect, which protects the child from unpleasant and painful experiences at induction. The need for an anticholinergic drug and its method of administration has to be decided separately. Respiratory depression was not observed clinically in this study. On the other hand Catchlove and Kafer (1971) demonstrated respiratory depression following diazepam $0.14\,\mathrm{mg\,kg^{-1}}$ i.v.

We must emphasize that pharmacological premedication is only one part of the preparation of a child for anaesthesia and surgery. In adults a preoperative visit has been shown to play an important role in the alleviation of apprehension and fear (Leigh, Walker and Janaganathan, 1977). The personal influence of the anaesthetic staff is even more important for a child (Doughty, 1959). Preoperative preparation must include not only diazepam as a rectal solution but also compassionate advice from a sympathetic anaesthetic team. Quiet surroundings and careful induction of anaesthesia under the influence of diazepam are beneficial.

We conclude that diazepam solution is absorbed effectively from the rectal mucosa and the pharmacokinetic behaviour of the drug nearly corresponds to that following i.v. injection. Because of rapid and effective absorption, rectal diazepam solution can not only replace tablet and suppository forms, but also the unreliable i.m. injection (Dundee, Gamble and Assaf, 1974; Hillestad et al., 1974). A dose of 0.4–$0.5\,\mathrm{mg\,kg^{-1}}$ is recommended and this can safely be repeated if the effect is inadequate. However, the child must be observed carefully. Diazepam solution can be used also for some types of short procedure.

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DIAZEPAM EN SOLUTION RECTALE EN TANT QUE MEDICATION PREOPERATOIRE POUR LES ENFANTS EN SE PREOCCUPANT TOUT SPECIALEMENT DES CONCENTRATIONS DANS LE SERUM

RESUME

L'absorption de diazépam en solution rectale a été étudiée sur 22 enfants âgés de 1 à 9 ans en mesurant les concentrations dans le sérum. La dose moyenne a été de $0{,}27 \pm 0{,}09\,\mathrm{mg\,kg^{-1}}$. La concentration moyenne dans le sérum a été de $98{,}5 \pm 53{,}5\,\mathrm{ng\,ml^{-1}}$, 4 min après l'administration et de $206{,}7 \pm 105{,}8\,\mathrm{ng\,ml^{-1}}$ après 11 min. La corrélation entre dose et concentration dans le sérum a été significative du point de vue statistique dans les deux cas. Avec une dose de $0{,}4$–$0{,}5\,\mathrm{mg\,kg^{-1}}$, nous avons obtenu une concentration adéquate dans le sérum dans les 5 à 6 min. Nous n'avons observé aucun effet secondaire. La solution rectale est un moyen d'administration plus rapide, plus efficace, et plus fiable que les cachets et les suppositoires, et même que les injections intramusculaires de diazépam dont les résultats sont incertains. Il est important de donner des soins méticuleux.

DIAZEPAM IN MASTDARM-LÖSUNG ALS PRÄMEDIKATION FÜR KINDER, SPEZIELL IN BEZUG AUF SERUMKONZENTRATIONEN

ZUSAMMENFASSUNG

Die Absorption einer Diazepam-Mastdarmlösung wurde bei 22 Kindern im Alter von 1–9 Jahren durch Messung der Serumkonzentrationen studiert. Die mittlere Dosis betrug $0{,}27 \pm 0{,}09\,\mathrm{mg\,kg^{-1}}$. Die mittlere Serumkonzentration 4 Minuten nach Verabreichung betrug $98{,}5 \pm 53{,}5\,\mathrm{ng\,ml^{-1}}$ und 11 Minuten nach der Verabreichung $206{,}7 \pm 105{,}8\,\mathrm{ng\,ml^{-1}}$. Die Korrelation zwischen Dosis und Serumkonzentration zu beiden Zeiten war statistisch bedeutend. Bei einer Dosis von $0{,}4$–$0{,}5\,\mathrm{mg\,kg^{-1}}$ wurde eine hinreichende Serumkonzentration innerhalb 5–6 Minuten erreicht. Es wurden keinerlei Seiteneffekte beobachtet. Eine Mastdarmlösung stellt eine schnellere, wirksamere und zuverlässigere Alternative für Tabletten und Zäpfchen dar, und für die unberechenbare intramuskuläre Injektion mit Diazepam. Sorgfältige Krankenpflege ist sichtig.

ABSORCION DE SOLUCIONES DE DIAZEPAN POR PARTE DEL RECTO COMO PREMEDICACION PARA NIÑOS, CON REFERENCIA ESPECIAL A LAS CONCENTRACIONES EN EL SUERO

SUMARIO

Se estudió en 22 niños, con edades comprendidas entre 1 y 9 años, la absorción de soluciones de diazepan por parte del recto, midiendo las concentraciones en el suero. La dosis media fue de $0{,}27 \pm 0{,}09\,\mathrm{mg\,kg^{-1}}$. La concentración media en el suero fue de $98{,}5 \pm 53{,}5\,\mathrm{ng\,ml^{-1}}$, a los cuatro minutos después de la administración, y de $206{,}7 \pm 105{,}8\,\mathrm{ng\,ml^{-1}}$ a los 11 min. La correlación entre la dosis y la concentración en el suero fue estadísticamente significativa en ambas ocasiones. Con una dosis de $0{,}4$–$0{,}5\,\mathrm{mg\,kg^{-1}}$ se logró una concentración en el suero adecuada en el plazo de 5–6min. No se observaron efectos secundarios. Una solución rectal provee una opción más rápida, más efectiva y más fiable que las tabletas y los supositorios y que la incierta inyección intramuscular de diazepan. El cuidado meticuloso es importante.

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GLYCOPYRROLATE IN CHILDREN

P. WARRAN, P. RADFORD AND M. L. M. MANFORD

SUMMARY

The effects of glycopyrrolate 10 μg kg^{-1} i.v. given at induction of anaesthesia were compared with those of atropine 20 μg kg^{-1} i.v. given at induction and oral atropine 30 μg kg^{-1} given 90 min before operation. Antisialagogue effect, changes in axillary temperature, heart rate, frequency of cardiac arrhythmia and postoperative restlessness were determined. Patients who had received oral atropine had more pharyngeal secretions, a lower heart rate and a greater frequency of cardiac arrhythmia than when either atropine or glycopyrrolate was given i.v. Secretions were significantly less during operation when i.v. glycopyrrolate was used.

Despite its declining use in adults anticholinergic premedication is required frequently in children especially before ophthalmic or ear, nose and throat surgery. Glycopyrrolate (Robinul) is a recently introduced quaternary ammonium anticholinergic agent with powerful and prolonged antisialagogue activity (Mirakhur, Dundee and Jones, 1978). Although a number of studies report its use as preanaesthetic medication in adults (Mirakhur et al., 1978; Cozanitis, Dundee and Khan, 1980; Sengupta, Gupta and Pandey, 1980), little information exists on its efficacy in paediatric patients.

In the present study, the effects of glycopyrrolate and atropine, administered by i.v. injection, have been compared. Since, in this hospital, those children given oral premedication usually receive oral atropine, a group of patients receiving this form of medication was studied.

PATIENTS AND METHODS

Sixty-nine children, aged 2–12 yr and weighing less than 50 kg, were included in the trial. They underwent elective ear, nose and throat or eye surgery under endotracheal anaesthesia.

Oral premedication with diazepam 0.25 mg kg^{-1} was given approximately 90 min before operation. Each patient was randomly allocated to one of three groups: (1) oral atropine 30 μg kg^{-1}, with the diazepam; (2) glycopyrrolate 10 μg kg^{-1} i.v.; (3) atropine 20 μg kg^{-1} i.v. (at the induction of anaesthesia in the case of groups (2) and (3)). The i.v. agents were administered double-blind. For ethical reasons, an unpremedicated control group was not included.

If the child was awake in the anaesthetic room, anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. If the patient was asleep, anaesthesia was induced with nitrous oxide in oxygen and halothane. The antisialagogue was given i.v. immediately on loss of consciousness. Intubation of the trachea was facilitated with suxamethonium 1 mg kg^{-1} i.v. and anaesthesia was maintained with nitrous oxide in oxygen and halothane. Respiration was spontaneous throughout the procedure. Dihydrocodeine 1 mg kg^{-1} was given i.m. during surgery to patients thought likely to have pain after operation.

Dryness of the mouth was assessed at induction, during the operation and in the recovery ward. The mouth and pharynx were graded as "wet" or "dry" depending upon whether suction was needed or not. Axillary temperature was recorded, using a glass thermometer, before, during and following surgery.

The electrocardiogram was monitored continuously throughout the operation. Any arrhythmia was noted and recorded for later analysis. Heart rate was recorded before or at the time of premedication, at the beginning of surgery, on return to the recovery ward and 30 min after operation. An assessment as to whether each child was asleep, calm or restless was made by the staff of the recovery ward.

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Non-parametric statistical analyses were carried out using Fisher's exact test; parametric data were analysed by *t* test.

RESULTS

The three groups were similar in respect of age, sex, weight, type of operation and use of analgesics during operation (table I).

There were no differences in salivation between the groups at induction. However, patients in the glycopyrrolate group were significantly dryer than the oral atropine group during operation ($P = 0.048$). The i.v. atropine group was dryer than the oral atropine group, but this difference was not statistically significant. Two of the patients in the i.v. atropine group and one in the oral atropine group were classified as "extremely wet" by the anaesthetist. There were no significant differences between the groups in the period after surgery.

The data from the patients undergoing operations on the throat (tonsillectomy and adenotonsillectomy) were analysed separately. There were no marked differences in respect of this sub-group compared with the group as a whole, except in the oral atropine group in which 60% of the patients undergoing throat surgery were "wet" during surgery, compared with 30% of the remaining patients.

TABLE I. *Physical characteristics of the patients studied in each of the three groups. Mean ± SEM are shown for age and weight.* *"Other" *includes ear and eye surgery.* †*DHC = Dihydrocodeine*

Group	No.	Sex		Operation		Age (yr)	Weight (kg)	No. receiving intraoperative DHC†
		M	F	Throat	Other*			
Glycopyrrolate (i.v.)	26	18	8	13	13	6.5±0.6	23.7±1.7	18
Atropine (i.v.)	21	10	11	10	11	7.2±0.6	27.9±2.7	13
Atropine (oral)	22	14	8	10	12	6.3±0.6	23.2±1.7	15

TABLE II. *Effects on heart rate, temperature and salivation.* * *Significant differences* ($P<0.05$)

Group	No.	Mean heart rate (beat min^{-1} ± SEM)			
		Pre-op.	Intra-op.	Post-op.	30 min post-op.
Glycopyrrolate (i.v.)	26	99±2.3	141±3.2*	126±3.6	120±3.3
Atropine (i.v.)	21	96±2.5	137±3.3*	130±4.0	117±3.5
Atropine (oral)	22	96±3.3	124±4.3	121±4.5	116±2.9

Group	No.	Mean axillary temperature (°C ± SEM)		
		Pre-op.	Intra-op.	Post-op.
Glycopyrrolate (i.v.)	26	36.6±0.075	36.7±0.087	36.4±0.1
Atropine (i.v.)	21	36.5±0.079	36.8±0.770	36.6±0.084
Atropine (oral)	22	36.6±0.085	36.8±0.079	36.5±0.091

Group	No.	Antisialagogue effect (number of patients)					
		Induct		Intra-op.		Post-op.	
		Wet	Dry	Wet	Dry	Wet	Dry
Glycopyrrolate (i.v.)	26	10	16	4	22*	6	20
Atropine (i.v.)	21	9	12	3	18	2	19
Atropine (oral)	22	5	17	10	12	9	13

Although patients in the oral atropine group were often flushed, there were no significant differences in body temperatures between the three groups.

Heart rate increased in all groups following the induction of anaesthesia and the beginning of surgery. Patients in the glycopyrrolate and i.v. atropine groups had significantly faster heart rates during surgery than did the patients in the oral atropine group ($P < 0.05$ and 0.005 respectively). In two patients (one from the glycopyrrolate group and one from the oral atropine group) heart rate decreased to less than 70 beat min^{-1}. There was no difference in heart rate response in those patients receiving analgesics after operation.

Twenty-one arrhythmias were observed in 17 patients; 41% of the oral atropine group compared with 19% of each of the other groups. This difference was not statistically significant. Most of the arrhythymias were episodes of frequent ventricular ectopic beats. One 6-yr-old patient undergoing tonsillectomy who had received i.v. atropine presented with ventricular ectopic beats which were sufficiently worrying to require treatment with lignocaine.

The majority of the patients slept peacefully following operation. Atropine was not associated with more restlessness after operation than was glycopyrrolate.

DISCUSSION

Several reports have shown that glycopyrrolate is more potent than atropine as an antisialagogue (Wyant and Kao, 1974; Mirakhur, Dundee and Jones, 1978). In the present study, most of the patients receiving glycopyrrolate or atropine i.v. were acceptably dry. However, several of the patients receiving orally administered atropine had unsatisfactory oropharyngeal secretions: it is clear from these findings that atropine 30 $\mu g\, kg^{-1}$ orally is less effective than 20 $\mu g\, kg^{-1}$ i.v. This suggests that the ratio of 1.86:1 reported by Murrin (1973) as the ratio between oral and i.m. dose is more appropriate than the ratio of 1.3:1 suggested by Joseph and Vale (1960).

None of the trial groups developed a significant mean increase in temperature, confirming the findings of Magbagbeola (1973) and Mirakhur, Dundee and Jones (1978) that, despite inhibition of sweating, atropine and glycopyrrolate do not significantly affect body temperature.

Heart rate has been used as an index of the vagal blocking action of anticholinergic drugs. This is an important consideration in children who require frequent administration of suxamethonium or who undergo squint surgery (Leigh et al., 1957; Cozanitis, Dundee and Khan, 1980). Heart rates of children in the oral atropine group were significantly slower than the rates for the other groups, suggesting a less effective vagal blocking action.

The use of atropine can be associated with cardiac arrhythmia during paediatric anaesthesia (Thurlow, 1972). There have been several reports suggesting that glycopyrrolate is less likely to produce changes in rhythm (Mirakhur et al., 1978). In the present study, cardiac irregularities occurred with the same frequency in both groups receiving i.v. premedication. The frequency was less, however, than that observed in the group receiving oral atropine, a group which also had excessive oral secretions and inadequate vagal block.

Because atropine is a tertiary amine and lipophilic, it crosses the blood–brain barrier and can cause restlessness and disorientation (the central anticholinergic syndrome). Glycopyrrolate is a quaternary amine and crosses the barrier to a limited extent (Proakis and Harris, 1978). However, the present study found no difference between the groups in the frequency of restlessness after operation.

Since the completion of this study, Lavis, Lunn and Rosen (1980) have published a study comparing the dose–effect relationship of glycopyrrolate and atropine as premedicants in paediatric patients. Although the maximum doses of glycopyrrolate and atropine were less than those used in the present study (5 $\mu g\, kg^{-1}$ and 10 $\mu g\, kg^{-1}$ respectively), broadly similar results were presented in terms of the relative effects of these drugs on heart rate and rhythm, and temperature. In the study of Lavis, Lunn and Rosen (1980), antisialagogue activity was not assessed at the induction of anaesthesia or during the operation.

The use of anticholinergic drugs in pre-anaesthetic medication has been questioned (Mirakhur et al., 1978). Children probably do need anticholinergic agents because of their tendency to salivate profusely and there is certainly a need if suxamethonium is to be used, or if there is to be surgery to the throat or eyes.

Where there is such an indication, glycopyrrolate is a satisfactory alternative to atropine.

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LE GLYCOPYRROLATE CHEZ LES ENFANTS

RESUME

Nous avons comparé les effets du glycopyrrolate administré par voie intraveineuse à raison de 10 µg kg^{-1} au moment de l'induction de l'anesthésie à ceux de l'atropine, aussi administrée par voie intraveineuse à raison de 20 µg kg^{-1} au moment de l'induction de l'anesthésie et à ceux de l'atropine administrée par voie buccale à raison de 30 µg kg^{-1} 90 min avant l'intervention chirurgicale. Nous avons déterminé les effets antisialogogues, les variations de température sous les aisselles, la fréquence cardiaque, la fréquence de l'arythmie cardiaque de même que la nervosité postopératoire. Les patients auxquels on avait administré de l'atropine par voie buccale ont eu davantage de sécrétions pharyngiennes, une fréquence cardiaque plus faible, et une plus grande fréquence d'arythmie cardiaque que lorsque l'atropine ou le glycopyrrolate a été administré par voie intraveineuse. Les sécrétions ont été nettement miondres pendant l'opération lorsque du glycopyrrolate avait été administré par voie intraveineuse.

GLYCOPYRROLAT BEI KINDERN

ZUSAMMENFASSUNG

Die Auswirkungen von Glycopyrrolat 10 µg kg^{-1}, intravenös bei der Einleitung der Anästhesie verabreicht, wurden mit den Auswirkungen von Atropin 20 µg kg^{-1}, intravenös bei der Einleitung der Anästhesie verabreicht, und den Auswirkungen von oralem Atropin 30 µg kg^{-1} 90 Minuten vor der Operation verglichen. Der speichelflusshemmende Effekt und Änderungen der Achseltemperatur, des Herzschlags und der Frequenz von Arrhythmie und postoperativer Ruhelosigkeit wurden bestimmt. Patienten, die orales Atropin bekommen hatten, zeigten mehr Rachensekretionen, einen niedrigeren Herzschlag und eine grössere Frequenz von Arrhythmie als bei der intravenösen Verabreichung von Atropin oder Glycopyrrolat. Sekretionen während der Operation waren bedeutend weniger, als Glycopyrrolat intravenös verabreicht wurde.

GLICOPIRROLATO ADMINISTRADO A NIÑOS

SUMARIO

Se compararon los efectos de 10 µg kg^{-1} de glicopirrolato intravenoso, administrado durante la inducción de la anestesia, con relación a los efectos ocasionados por 20 µg kg^{-1} de atrofina intravenosa administrada durante la inducción y con 30 µg kg^{-1} de atropina oral, administrada 90 min antes de la operación. Se determinaron el efecto antisialagogo, cambios en la temperatura axilar, el ritmo cardiaco, la frecuencia de la arritmia cardiaca y la inquietud posoperativa. Los pacientes que recibieron atropina oral presentaron más secreciones faringeas, un ritmo caridaco inferior y una mayor frecuencia de arritmia cardiaca que cuando se administraron intravenosamente la atropina o el glicopirrolato. Cuando se usó el glicopirrolato intravenoso, las secreciones fueron significativamente menores durante la operación.

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EFFECTS OF GLYCOPYRROLATE AND ATROPINE COMBINED WITH ANTACID ON GASTRIC ACIDITY

R. E. Roper and M. G. Salem

SUMMARY

Glycopyrrolate, atropine or saline were administered i.v. with oral magnesium trisilicate 1 h before induction of anaesthesia to patients about to undergo Caesarean section. Both anticholinergics greatly reduced gastric acidity. It is suggested that glycopyrrolate should be used in combination with antacid therapy before obstetric anaesthesia and puerperal tubal ligation because of its prolonged duration of action, effect on gastric secretion and failure to cross the placental barrier.

Despite recent advances in anaesthesia and a great reduction in frequency of postoperative morbidity and mortality, aspiration of acidic gastric contents still accounts for a considerable number of deaths associated with obstetric anaesthesia. The eighth Confidential Enquiry into Maternal Deaths in England and Wales, 1973–1975 (Tomkinson et al., 1979) reported that 13 deaths were caused by inhalation of stomach contents. Nine of these patients had received routine antacid therapy and yet subsequently died of Mendelson's syndrome.

A competant anaesthetist using a safe technique, particularly during induction, with application of cricoid pressure and rapid tracheal intubation is obviously a prerequisite, but despite this, reduction in gastric acidity is still a valuable safeguard. Simple antacid régimes may not achieve sufficient neutralization of stomach contents in every patient and anticholinergic drugs and, recently, cimetidine have been assessed for ability to reduce gastric acidity. We report here the effects, in patients undergoing Caesarean section, of combined administration of antacid with either atropine or the newer quaternary ammonium anticholinergic, glycopyrrolate.

METHODS

Patients

Healthy female patients about to undergo elective Caesarean section were studied after giving consent. None was given drugs with pronounced anticholinergic activity in the preceding 24 h.

Anaesthetic technique

All patients received magnesium trisilicate mixture BPC 20 ml orally about 60 min before induction of anaesthesia. At the same time, they received 1 ml of either sodium chloride injection, atropine injection 0.4 mg ml^{-1} or glycopyrrolate 0.2 mg ml^{-1} i.v. Patients were allocated randomly to the three treatment régimes which were administered under double-blind conditions. Following preoxygenation, induction of anaesthesia was performed with methohexitone 1 mg kg^{-1}, cricoid pressure and suxamethonium 100 mg. An endotracheal tube was inserted and anaesthesia maintained with nitrous oxide and oxygen. Relaxation was maintained with alcuronium 15 mg. Immediately after delivery, ergometrine 0.5 mg was given to increase uterine tone and phenoperidine 2 mg to deepen the level of anaesthesia. Atropine 1.2 mg and neostigmine 5.0 mg were given to antagonize residual neuromuscular blockade at the end of the operation.

Assessment

Gastric juice was aspirated immediately after induction and immediately before antagonism of the neuromuscular block. Fetal heart rate was recorded with a Sonicaid before administration of the drug under study and at 10-min intervals until delivery; neonatal heart rate was measured 10 min after delivery. The Apgar score was recorded 1 min and 5 min after delivery.

RESULTS

One hundred and twenty-seven patients took part in the study; they were well matched for age, weight and time from administration to induction of the drugs under study (table I). Distribution of gastric pH and the mean values immediately

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TABLE I. *Details of the patients studied* (*mean* ± SEM)

	Placebo	Atropine	Glyco-pyrrolate
Number	42	45	40
Age (yr)	29±1.1	28±0.7	27±0.9
Weight (kg)	72±1.4	72±1.6	73±1.7
Time from pre-med. to induction (min)	64±1.8	63±1.9	60±2.3

following induction and before antagonism of the neuromuscular block are shown in figure 1. The difference in frequency between both anticholinergic groups and the placebo group was significant ($P < 0.00001$ after induction; $P < 0.005$ before antagonism of neuromuscluar block; Fisher's exact test). It was not possible to obtain gastric juice samples from every patient studied.

Fetal heart rate in both anticholinergic groups and the placebo group did not change significantly (mean change < 3 beat min^{-1} from the pre-administration value). Similarly, there was no significant difference in mean neonatal heart rate or in Apgar scores between the three groups.

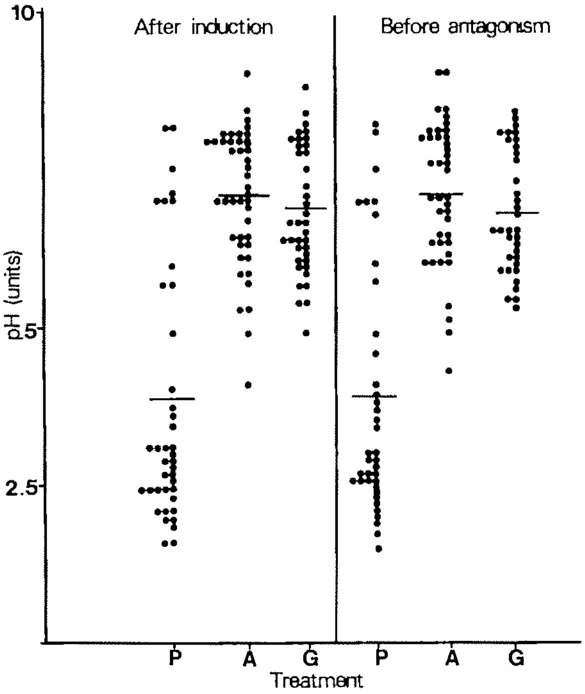

FIG 1. Values of gastric juice pH immediately following induction and before antagonism of neuromuscular block in those patients receiving placebo (P), atropine (A) or glycopyrrolate (G). The horizontal lines indicate mean values.

DISCUSSION

The present study has shown that the co-administration of atropine and glycopyrrolate with magnesium trisilicate provides acceptable gastric pH immediately before anaesthesia and after antagonism of neuromuscular blockade. It also confirms the unsatisfactory control of acidity produced by magnesium trisilicate alone which has been suggested previously (Peskett, 1973). The overall frequency of patients in our study with a pH of less than 2.5 after having received magnesium trisilicate 20 ml (35%) is similar to that reported by Taylor and Pryse-Davies (1966) in a control series of patients (42%).

Reports on the effects of glycopyrrolate alone on gastric acidity is equivocal. Keating, Black and Watson (1978) showed that glycopyrrolate 0.4 mg i.m. given to non-obstetric patients 60 min before operation had very little effect on gastric pH. Similarly, Stoelting (1978) showed that administration of morphine and glycopyrrolate 0.2 mg was not significantly different from administration of morphine alone in decreasing gastric acidity immediately following induction. However, Baraka and others (1977) demonstrated in parturient patients that administration of glycopyrrolate 0.4 mg i.m. produced a reduction in gastric acidity which was significantly different from that produced by atropine.

These differences in published data are difficult to explain but may be related to differences in patients studied and routes of administration. Although Baraka and others (1977) found a significant effect of glycopyrrolate, the dose they used was twice that (0.2 mg) normally used for premedication and would be likely to produce an unpleasant antisialagogue effect for a considerable duration after operation. We administered antacid and anticholinergics together to determine any synergism which would permit reduction of the amount of anticholinergics administered before operation and to use a route of administration which provides complete availability of the drugs. In addition, we administered the anticholinergics 60 min before induction; a period which, according to Baraka and others (1977), is necessary to achieve maximum effect. The significant findings presented are in good agreement with those of Boatright and others (1970), who administered glycopyrrolate with a magnesium hydroxide–aluminium hydroxide antacid mixture to paediatric patients and showed marked synergism between the two drugs. The samples with high gastric pH obtained in our placebo group may have resulted from regurgitation of duodenal contents into the stomach.

Although both atropine and glycopyrrolate were equally effective in the present study, glycopyrrolate possesses theoretical advantages in obstetric anaesthesia. Because it is a quaternary ammonium compound, it is highly lipophobic and penetrates with difficulty through lipid membranes such as the blood–brain and placental barriers. Proakis and Harris (1978) showed that, in the dog, a peak fetal serum : maternal serum concentration ratio of only 0.04 was achieved after the administration of glycopyrrolate, whereas this ratio was 1.0 after the administration of atropine. Heyman and others (1976) showed clinically that glycopyrrolate 0.4 mg administered to the mother had no significant effect on fetal heart rate, whereas the administration of atropine 0.8 mg produced a significant increase in fetal heart rate.

In conclusion, we have shown that both glycopyrrolate and atropine administered i.v. with oral magnesium trisilicate produce a more favorable gastric pH. On a theoretical basis, glycopyrrolate offers greater safety to the fetus and, having a longer duration of action, is thus the preferred agent for use in obstetric anaesthesia. Antacid therapy with magnesium trisilicate alone is unsatisfactory for use in routine premedication of obstetric patients and anaesthetists should administer an anticholinergic, preferably glycopyrrolate, i.v. 1 h before anaesthesia rather than giving it immediately before induction.

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EFFETS DU GLYCOPYRROLATE ET DE L'ATROPINE COMBINES AVEC UN ANTACIDE SUR L'ACIDITE GASTRIQUE

RESUME

Il a été administré du glycopyrrolate, de l'atropine ou de l'eau physiologique par voie intraveineuse, de même que du trisilicate de magnésium par voie buccale, une heure avant l'induction de l'anesthesie à des patientes sur le point de subir une césarienne. Les deux anticholinergiques ont grandement réduit l'acidité gastrique. Ceci laisse penser que le glycopyrrolate doit être utilisé en combinaison avec un traitement antacide avant toute anesthésie pour une intervention obstétrique et pour toute ligature tubulaire puerpérale, en raison de sa durée prolongée, de son effet sur la sécrétion gastrique et du fait qu'il ne traverse pas la barrière placentaire.

AUSWIRKUNGEN VON GLYCOPYRROLAT UND ATROPIN IN VERBINDUNG MIT EINEM SÄUREBINDENDEN MITTEL AUF DIE MAGENSÄURE

ZUSAMMENFASSUNG

Glycopyrrolat, Atropine oder eine Salzlösung wurde intravenös in Verbindung mit oralem Magnesiumtrisilikat 1 Stunde vor der Einleitung der Anästhesie bei Patienten verabreicht, die sich gerade einem Kaiserschnitt unterzogen. Beide anticholinergische Mittel führten zu einer beträchtlichen Verminderung der Magensäure. Es wird vorgeschlagen, Glycopyrrolat in Verbindung mit einer säurebindenden Technik vor der Geburtsanästhesie und Puerperaltubenligatur zu verwenden, auf Grund seiner ausgedehnten Wirkungsdauer, seiner Wirkung auf Magensekretionen und seiner Unfähigkeit, die Plazentarschranke zu überschreirten.

EFECTOS DEL GLICOPIRROLATO Y DE LA ATROPINA EN COMBINACION CON ANTIACIDO SOBRE LA ACIDEZ GASTRICA

SUMARIO

Se administraron intravenosamente glicopirrolato, atropina o soluciones salinas, junto con trisilicato de magnesio via oral,

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PLASMA PROTEIN CONCENTRATION AND RECOVERY FROM ANAESTHESIA IN MAN

G. TORRI, L. STELLA, G. PRADELLA, E. MAESTRONE AND C. MARTANI

SUMMARY

The effect of the concentration of plasma protein on the recovery from anaesthesia induced by equipotent doses (UD_{95}) of thiopentone and Althesin was studied in 48 patients. The recovery time (RT) was plotted against the concentrations of total plasma proteins (TPP) and albumin (Al). A small decrease in TPP concentration from normal range affected the recovery time minimally; a small decrease in TPP concentration from a low basal value markedly increased the recovery time with both agents. A large decrease in TPP concentration increased the recovery time from thiopentone and Althesin markedly.

Following a single i.v. administration of an anaesthetic agent recovery from anaesthesia depends on the redistribution of the agent from brain to high capacity tissues (Price et al., 1960), and on renal clearance and biodegradation. Furthermore, the activity and fate of anaesthetics are intimately linked to the degree of binding to plasma proteins, since this determines the amount of drug available to the tissues.

The quantity of the anaesthetic bound to proteins is dependent on many factors: pH of blood (Goldbaum and Smith, 1954), the age of the patient (Pruitt and Dayton, 1971), and the presence of other drugs or metabolites which may displace the anaesthetic drug from binding sites (Dundee and Richards, 1954; Odel, 1959; Anton, 1960, 1961; Lasser, Elizondo-Martel and Granke, 1963; Pagnini et al., 1971; Gillette, 1973; Ghoneim et al., 1976).

In clinical practice a decrease in the concentrations of the plasma proteins is often associated with liver or kidney disease. Since these two organs are involved also in the elimination of the anaesthetic, the part played by the concentration of protein *per se* on the recovery time from anaesthesia is difficult to evaluate.

In this study the effect of the concentrations of the total plasma proteins (TPP) and albumin (Al) on the recovery time (RT) has been investigated in man using two anaesthetic agents: thiopentone and Althesin, which have protein-binding fractions of 0.75 (Goldbaum and Smith, 1954) and 0.4 (Jones, 1972) respectively.

PATIENTS AND METHODS

Two groups of 24 patients, (20–50 yr) of both sexes, were studied. Informed consent was obtained from each patient.

The patients were allocated in random fashion to receive thiopentone or Althesin for surgical dressings requiring very short and light anaesthesia. In all patients BUN concentration, bilirubin concentration, liver and kidney function, acid–base balance, e.c.g., arterial pressure and circulatory time were physiological. No patient had received any drug which interacted with protein binding or anaesthetic activity during the period before operation.

Premedication (atropine 0.007 mg kg^{-1}) was administered before the induction of anaesthesia. The equipotent doses required to produce unconsciousness in 95% of patients (UD_{95}) were used (thiopentone 2.619 mg kg^{-1}, Althesin 0.284 mg kg^{-1}) (Stella, Torri and Castiglioni, 1979) and the technique of injection standardized as proposed by Clarke and colleagues (1968). The UD_{95} was injected over 30 s to an antecubital vein following active hyperaemia obtained by inflation of a sphygmomanometer cuff to 300 mm Hg for 2 min. During the injection the patient was asked to count aloud and when this stopped he was asked to respond to a simple command: "open your eyes".

If a response was not obtained the patient was stated to be asleep, and from this moment until the

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patient was able to respond to the same command was determined—the recovery time.

The few patients that remained awake after receiving the UD_{95} were excluded from the study.

The relationship between recovery time and total plasma proteins concentration (RT/TPP) and recovery time and albumin concentration (RT/Al) were determined by the method of least squares. Both linear and exponential correlations were determined to find the best fit for the experimental data.

RESULTS

The two groups of patients were comparable for age and sex. In the thiopentone group the mean age was 42.08 ± 8.29 and in the Althesin group 38.42 ± 10.25 yr ($t = 1.62$; n.s.). The first group included 11 males and 13 females; the second group 10 males and 14 females ($\chi^2 = 0.08$; n.s.).

Figure 1 shows the correlations RT/TPP and RT/Al for thiopentone and Althesin. The best fits of the RT/TPP and RT/Al relationships are represented by the exponential correlations shown.

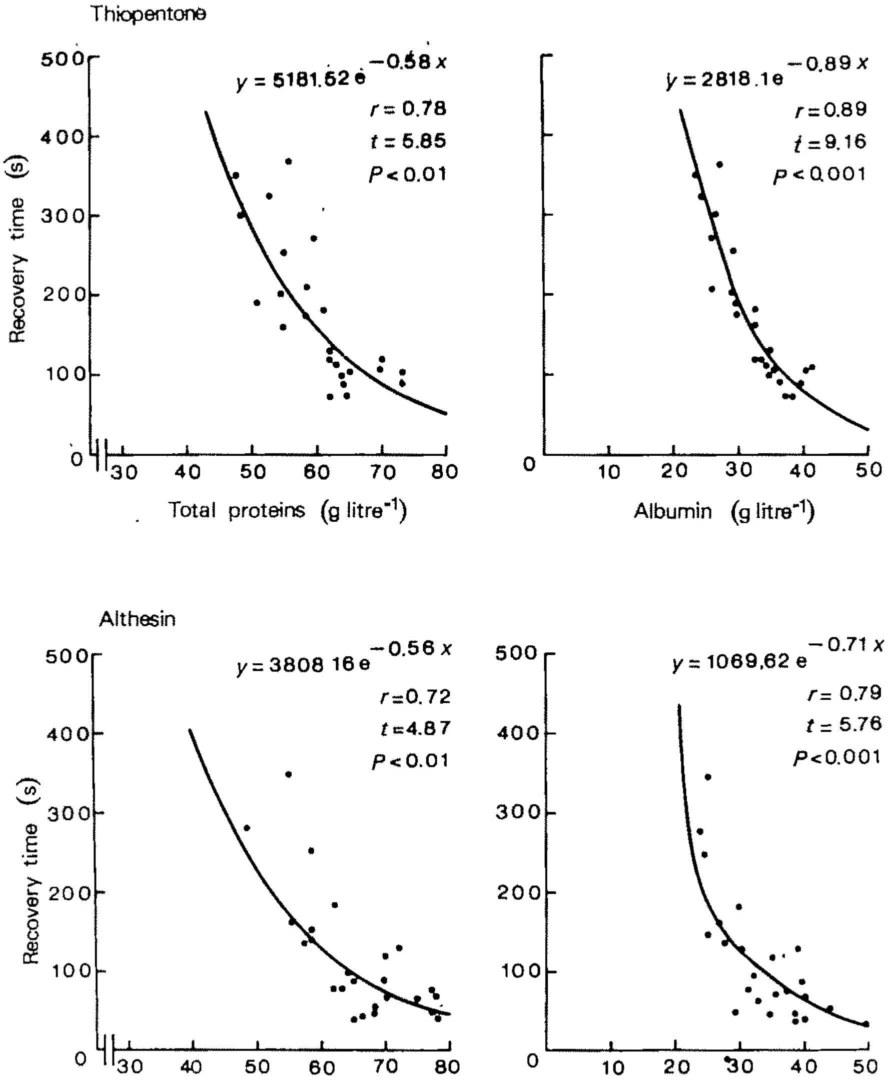

FIG. 1. Relationship between recovery time and total plasma protein or albumin concentrations for thiopentone and Althesin.

Using UD_{95}, at a normal value of TPP of 70 g litre^{-1}, the recovery time was shorter with Althesin (76 s) than with thiopentone (103 s).

However, it appeared that the lower the TPP concentration the longer the recovery time with both anaesthetics. Because of the particular shape of the relationships the same change in TPP concentration affected the recovery time to a different extent at normal and low values of TPP. A small change in TPP concentration within the normal range did not affect the recovery time significantly, whereas at very low values of TPP a further small decrease may increase the recovery time markedly.

When the changes in TPP concentration were large, it was observed that, despite their different protein binding fraction, the two anaesthetics had similar effects. In fact, when the concentration of TPP was decreased to 50 g litre^{-1} recovery time was three times greater than that observed at TPP value of 70 g litre^{-1} for both agents.

The statistical analysis of the correlation coefficients (r) of the RT/TPP and RT/Al relationships indicates that the best correlation was found for RT/Al both for thiopentone ($t = 5.58$; $P < 0.001$) and Althesin ($t = 4.64$; $P < 0.001$).

DISCUSSION

Many previous studies have investigated the displacement of i.v. anaesthetics from their binding sites by other drugs and the consequent increase in anaesthetic activity. In the present study an increase in anaesthetic activity was observed as a result of a decrease in the concentration of TPP and of the subsequent increase in the amount of free drug.

Since we used two anaesthetics which differ in their protein binding fractions, different effects were expected. The results indicate that the changes in recovery time were similar with both anaesthetics when identical decreases in TPP concentration were considered. Since thiopentone is bound extensively to plasma proteins, and Althesin to a lesser extent, a similar decrease in TPP concentration results in a larger amount of free drug with thiopentone than with Althesin. Nevertheless, since Althesin has an anaesthetic potency 10 times greater than thiopentone (Stella, Torri and Castiglioni, 1979) this increases the clinical effect of the smaller increase in unbound drug. Thus, although in theory the action of an anaesthetic with a low protein-binding fraction should be affected little by changes in the concentration of TPP, in practice, this advantage may be counteracted by the high potency of the drug.

The best correlations pertained to the RT/Al relationship, a result which seems to confirm that albumin plays the most important role in binding anaesthetic agents. In spite of this we have stressed the correlation between RT/TPP because (1) albumin is not the only binding site for anaesthetics, as Althesin may be bound to other proteins such as lipoproteins or immunoglobulins (Jones, 1972); (2) usually every change in albumin concentration is associated with a proportional change in the concentration of TPP.

The use of the equipotent dose UD_{95} allowed us to obtain comparable results from the two anaesthetics, to avoid total saturation of the protein binding sites, and to avoid large decreases in ventilation with consequent changes in arterial pH.

Significant changes in the concentrations of TPP or albumin must be considered important factors which affect the recovery time from anaesthesia. In clinical practice this effect must be considered following acute blood loss, in undernourished patients and when haemodilution techniques are used.

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CONCENTRATIONS DE PROTEINES DANS LE PLASMA ET REPRISE DE CONSCIENCE APRES UNE ANESTHESIE CHEZ L'HOMME

RESUME

Nous avons fait une étude couvrant 48 patients et portant sur l'effet qu'ont les concentrations de protéines dans le plasma sur la reprise de conscience, après une anesthésie induite par des doses à efficacité égale (UD_{95}) de thiopentone et d'Althésine. Le temps nécessaire à la reprise de conscience (RT) a été porté sur un graphique de même que les concentrations totales de protéines dans le plasma (TPP) et l'albumine (Al). Toute petite diminution dans les concentrations de TPP par rapport à la plage normale n'a affecté que d'une manière minimale le temps nécessaire à la reprise de conscience; alors que toute faible diminution dans les concentrations de TPP par rapport à une faible valeur de base a fait augmenter très sensiblement le temps nécessaire à la récupération, dans le cas de ces deux agents. Toute importante diminution dans les concentrations de TPP a fait très nettement augmenter le temps nécessaire à la reprise de conscience après le thiopentone et l'Althésine.

PLASMAEIWEISSKONZENTRATION UND ERHOLUNG VON DER ANÄSTHESIE BEIM MENSCHEN

ZUSAMMENFASSUNG

Die Auswirkung der Plasmaeiweisskonzentration auf die Erholung von der durch gleichstarke Dosen (UD_{95}) von Thiopenton und Althesin induzierten Anästhesie wurde bei 48 Patienten studiert. Die Erholungszeit wurde gegen Gesamtplasmaeiweisskonzentrationen und Albumin aufgezeichnet. Eine kleine Verringerung der Gesamtplasmaeiweisskonzentration, ausgehend von dem normalen Bereich, hatte einen minimalen Einfluss auf die Erholungszeit; eine kleine Verringerung der Gesamtplasmaeiweisskonzentratione, ausgehend von einem niedrigen Basalwert, führte zu einer auffallenden Steigerung der Erholungszeit bei beiden Mitteln. Eine grosse Steigerung der Gesamtplasmaeiweisskonzentration führte zu einer auffallenden Steigerung der Erholungszeit bei Thiopenton und Althesin.

CONCENTRACION PROTEINICA EN EL PLASMA Y RECUPERACION DE LA ANESTESIA POR PARTE DEL HOMBRE

SUMARIO

Se estudió el efecto que en 48 pacientes ejerció la concentración proteínica del plasma en lo tocante a la recuperación de la anestesia inducida por dosis equipotentes (UD_{95}) de tiopentona y de Altesina. El tiempo de recuperación (RT) se trazó contra las concentraciones totales de proteina (TPP) y de albúmina (Al) en el plasma. Una pequeña disminución de la TPP con relación a la gama normal afectó minimamente al tiempo de recuperación; una pequeña disminución de la concentración de TPP a partir de un valor basal bajo aumentó notablemente el tiempo de recuperación con ambos agentes. Una gran disminución en la concentracion TPP aumentó notablemente el tiempo de la recuperación para la tiopentona y la Altesina.

Br. J. Anaesth. (1981), 53, 1285

CLOSED-CIRCUIT HALOTHANE AND ENFLURANE USING AN IN-CIRCLE GOLDMAN VAPORIZER

M. J. JORDAN AND J. A. BUSHMAN

SUMMARY

A closed-circle absorber system incorporating an in-circle Goldman vaporizer was used to administer halothane or enflurane in oxygen to adult patients. The attained inspired and end-tidal concentrations of volatile agent after a period of stabilization at each vaporizer setting were measured by mass spectrometry. During spontaneous respiration under halothane the ranges of inspired concentrations at settings 1, 1½ and 2 were respectively 0.5–0.9%, 1.4–2.4% and 3.3–4.5%. Corresponding inspired enflurane concentrations at the same settings were 0.8–1.4%, 1.9–2.8% and 3.7–5.0%. IPPV to 5% end-tidal carbon dioxide, although increasing the inspired concentrations slightly, produced considerable increases in end-tidal concentrations. Minimal pre-oxygenation was used to assess the problem of nitrogen accumulation within the circuit. The maximum nitrogen concentration was 56%.

The recent revival of interest in totally closed system anaesthetic techniques has produced a number of reviews of the associated advantages and disadvantages (Bushman et al., 1977; Adams, 1979). Recent work (Rayburn and Watson, 1980) suggests that, in patients who are artificially ventilated, the Bain system may provide better humidification of inspired gas, but circle-absorber systems used with basal fresh gas flows are unsurpassed in economy of gases and volatile agents, as well as freedom from pollution.

Non-rebreathing systems enable the inspired concentration to be held constant without difficulty. The alveolar concentration will increase towards the inspired concentration asymptotically with time at a rate that depends on the alveolar ventilation.

In circle-absorber systems, the relationship between ventilation and the inspired and alveolar concentrations developed is profoundly affected by the position of the vaporizer (Mapleson, 1960). If this is in the fresh gas supply line (VOC configuration) then the rate of supply of volatile agent to the circle is fixed and an increase in the patient's minute volume results in a decrease in inspired concentration. At basal flows of fresh oxygen, this effect negates the increase in alveolar concentration that would otherwise result from an increase in ventilation. As a result, the alveolar concentration is independent of ventilation over a wide range (Mushin and Galloon, 1960).

The vaporizer-in-circle (VIC) configuration, on the other hand, will deliver an increased inspired volatile concentration if the minute volume increases. This effect produces a sharp increase in alveolar concentration and deepening of anaesthesia as a result. Such a system can truly be described as self-regulating provided the patient continues to breathe spontaneously. By the same token, VIC systems are almost universally regarded as dangerous if the ventilation is controlled (Churchill-Davidson, 1978).

The fact that, short of measurement, there is no way of knowing the precise volatile concentration within the system at any given time, is probably the largest single obstacle to the more widespread acceptance of VIC circuits into clinical practice. A large number of factors affect the volatile concentrations attained (table I) and while some of the quantities involved will be known, or at least constant and easily measurable, many, particularly

TABLE I. *Factors affecting the attained concentrations in closed-circuit systems with in-circuit vaporizer*

Physical/equipment factors	Patient factors
Blood–gas sol. coeff. of agent	Minute volume
Volatility of agent	$\dot{V}/\dot{Q}$ inequality
Vaporizer setting	Mixed venous concentrations
Temperature	Cardiac output and distribution
Agitation of vaporizer	Lean body mass
Uptake by rubber, soda-lime	

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those dependent on the physiology of the patient, will be changing with time, measurable only with difficulty, or may have to be assumed.

The physics of closed circuits has been subjected to mathematical analysis by a number of workers. Mapleson (1960) showed that the inhaled concentration of a volatile agent in any circle system is given by:

$$F\text{I} = \frac{\dot{V}_{\text{in an}}}{\dot{V}_{\text{out o}}(1-\theta/\dot{V})+\theta}$$

where $F\text{I}$ is the fractional inhaled concentration, $\dot{V}_{\text{in an}}$ is the rate of supply of anaesthetic vapour to the circle, $\dot{V}_{\text{out o}}$ is the rate at which oxygen is leaving the circle, $\dot{V}$ is the patient's minute volume and θ is the rate of uptake of the volatile agent per unit inspired concentration.

A number of modifications of this expression have appeared in later publications, and Jennings and Styles (1968) derived a form describing specifically the conditions in VIC circuits:

$$F\text{I} = F\text{V}\,\frac{\dot{V}}{(\dot{V}_{\text{in o}}-200)(1-\theta/\dot{V})+\theta}$$

where $F\text{V}$ is the "vaporizer concentration", in this context the amount by which the volatile concentration increases as the gas passes through the in-circle vaporizer, and $\dot{V}_{\text{in o}}$ is the fresh gas flow. The patient's oxygen uptake is assumed to be 200 ml min^{-1}, so it can be seen that when the supply is matched to the uptake (when the circle is closed) the expression will simplify considerably, although even then its practical application will require an assumption to be made about both θ and $F\text{V}$. With the type of uncalibrated vaporizer usually used in closed circuits, an accurate value for $F\text{V}$ will necessitate direct measurement.

Fortunately, the behaviour of closed circuits in practice is more predictable than the theory might suggest and many anaesthetists use halothane in VIC systems with no means of measuring the inspired concentration directly, merely by knowing the approximate concentration developed and adjusting the vaporizer to the patient's response.

The fact that enflurane has physical properties broadly similar to those of halothane (table II) has lead to the supposition that it might be suitable for use in existing apparatus. Despite this there has been little published work on closed-circuit anaesthesia with this agent. Jones and others (1979) have described its use in the Marrett head, but currently available equipment has not been examined in a truly closed-circuit configuration.

TABLE II. *Comparison of the physical properties of halothane and enflurane*

	Halothane	Enflurane
Vapour pressure 20 °C (mm Hg)	243	174
Concentration of Sat. Vap. (%)	32	23
MAC (%)	0.7	1.7
Blood–gas solubility coeff.	2.4	1.9
Oil–gas solubility coeff.	224	98

The object of this work was to evaluate the practicality of using enflurane in a closed VIC system using the Goldman vaporizer (Goldman, 1962) by comparing the attained inspired and end-tidal concentrations with those achieved using halothane in the same apparatus. The effect on these concentrations of carefully controlled IPPV to 5% end-tidal carbon dioxide was examined and some assessment made of the problem of nitrogen accumulation.

METHODS

The apparatus involved incorporated a Goldman vaporizer (Medishield) in the inspiratory limb of a circle based on a 1.8-kg soda-lime canister (Boyle Mk III BOC) and two 1-m lengths of breathing hose. A miniature pneumotachograph head (Accutach, McGaw Respiratory Therapy) was situated between the patient Y-piece and the endotracheal tube, with a side-arm for the sampling probe of a Medishield MS 2 mass spectrometer and multiplexer. The integrated pneumotachograph output and the mass spectrometer signals for nitrogen, carbon dioxide and the volatile agent were fed to four chart recorder channels. The instantaneous oxygen concentration was displayed on the front panel of the mass spectrometer but was not recorded. A scheme of this arrangement is shown in figure 1.

The circuit was adapted for IPPV by the replacement of the breathing bag with the patient valve of a Pneupac Model 2 ventilator–resuscitator. This pneumatic logic device, described elsewhere (Adams and Henville, 1977) is driven by a separate 400-kPa oxygen supply, and is used both to ventilate the circle and act as the source of fresh oxygen, the machine flowmeter shown at the top of figure 1 being turned off during

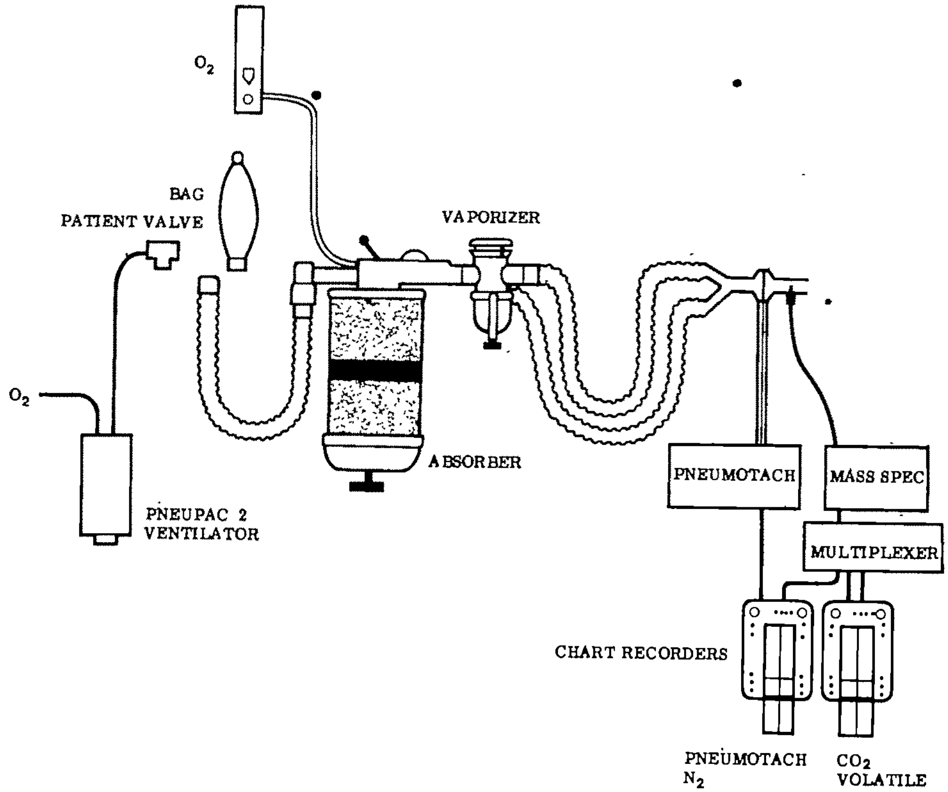

FIG. 1. Experimental apparatus.

IPPV. As the patient continues to take up oxygen, this will be replaced from the ventilator limb. As a result, instead of a symmetrical oscillation of gas within the ventilator limb, a stepwise net movement of gas towards the circle occurs. Provided the volume of the ventilator limb, in this case 1000 ml, is greater than the tidal volume then, even at the end of expiration, the volatile-laden contents of the circle never reach the patient valve exhaust port. Effectively, the circuit remains closed, venting only pure oxygen.

Patients were drawn from a heterogeneous pool of individuals ranging in age from 26 to 65 yr and in weight from 55 to 108 kg. Informed consent was obtained and they were randomly allocated to two groups of 10, to receive either halothane or enflurane via the system described. Measurements were made in the period before urological surgery.

Diazepam 10 mg was given by mouth 2 h before induction of anaesthesia. In the anaesthetic room an i.v. infusion of Hartmann's solution was started, e.c.g. electrodes applied and the arterial pressure measured then and subsequently every 1 min by automated oscillometry (Dinamap 845 Applied Medical Research).

Induction of anaesthesia was with thiopentone sodium until the loss of the lash reflex; this was followed by suxamethonium 1 mg kg^{-1}. The trachea was sprayed with 10% lignocaine and intubated. Apart from inflating the lungs with a few breaths of pure oxygen immediately before intubation, no attempt was made at preoxygenation and the circuit was kept closed from the start of the anaesthetic. The system was, however, flushed with oxygen immediately before induction, and tested rigorously for leaks. The fresh gas flow was adjusted to keep the bag adequately inflated.

Preliminary studies established that the useful range of delivered concentrations lay between settings 1 and 2 on the Goldman vaporizer for both agents. It was also found that, following an increase in vaporizer setting, a stable concentration within the circuit develops over approximately 5 min under spontaneous respiration, and rather faster during IPPV.

Thereafter the inspired concentration increases only very slowly. In the final plan, therefore, a period of 10 min was allowed for equilibration during spontaneous respiration and 5 min during IPPV.

The sequence of vaporizer settings used is shown in figure 2. Setting "1½", a point midway between settings 1 and 2, was found to be the minimum setting on which patients appeared to be anaesthetized at the beginning of an anaesthetic and was chosen as the starting point. Thereafter the plan was designed to ensure that the stable concentration was approached "from below" rather than while the concentration was decreasing. Settings 1, 1½ and 2 were evaluated during two periods of spontaneous respiration and settings 1 and 1½ during IPPV to 5% end-tidal carbon dioxide. The study ended as it began, with a period of spontaneous respiration at setting 1½, allowing comparison between the values attained under identical conditions separated by 40 min of anaesthesia. The within-patient correlation between the results obtained during these two periods was invariably to 0.2% of the volatile agent, for both inspired and end-tidal concentrations.

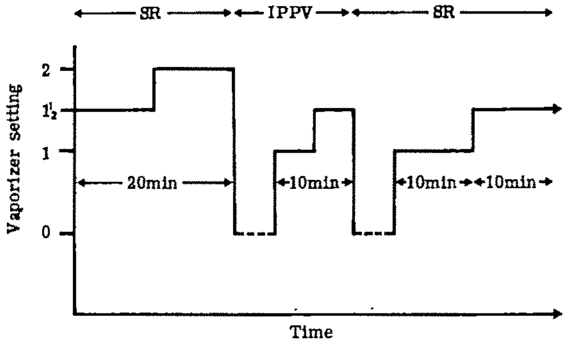

FIG. 2. Sequence of vaporizer settings used. During the periods shown by broken lines the inspired concentrations were allowed to decrease to less than 0.5%. SR = spontaneous respiration.

RESULTS

Figure 3 shows the inspired concentrations of halothane after the equilibration period at each vaporizer setting with spontaneous and controlled breathing. One obese individual was unable to breathe satisfactorily unassisted and data for the spontaneously breathing section of the study with halothane is based on nine patients. During

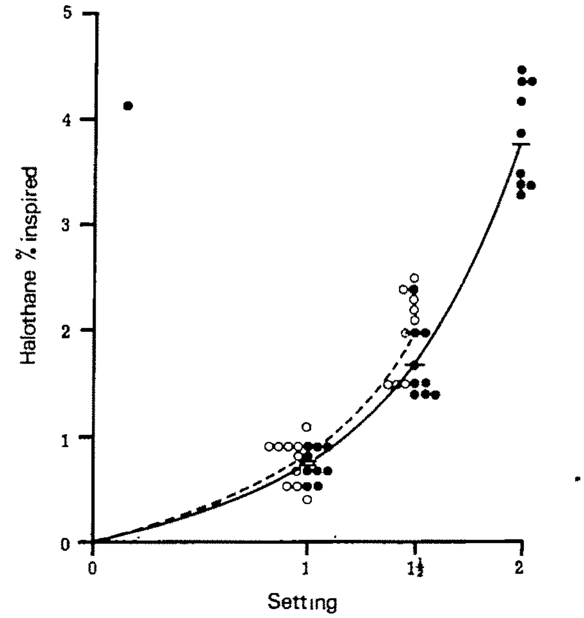

FIG. 3. Inspired halothane concentrations developed at the vaporizer settings evaluated. ● = mean values for spontaneous respiration (data from nine patients only), joined by continuous line. ○ = mean values during IPPV, joined by broken line.

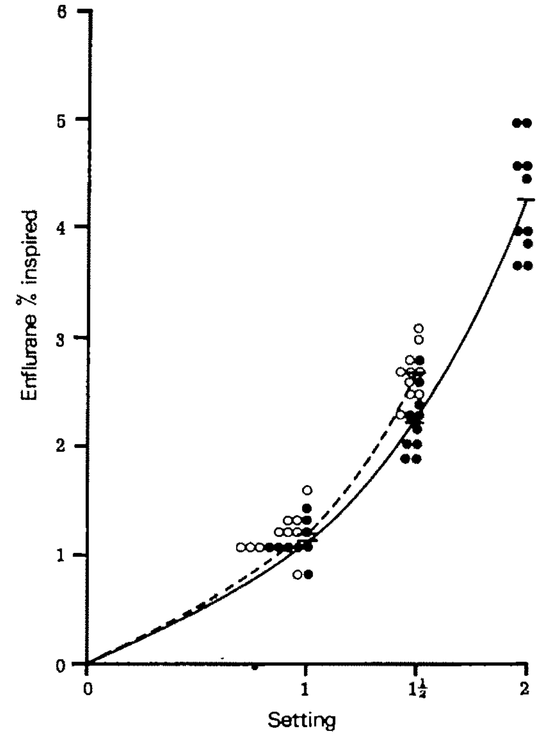

FIG. 4. Inspired enflurane concentrations. Data from 10 patients. (For legend see figure 3.)

spontaneous respiration, setting 1 provided between 0.5% and 0.9% halothane, setting 1½ 1.4–2.4% and setting 2 3.3–4.5%. These values were slightly increased by IPPV.

Figure 4 shows the same data for enflurane. Setting 1 delivered 0.8–1.4% inspired enflurane during spontaneous breathing, setting 1½ 1.9–2.8% and setting 2 3.7–5.0%, IPPV to normocapnia again producing a modest increase.

End-tidal concentrations for halothane are shown in figure 5, those for enflurane in figure 6. A much greater difference between spontaneous and controlled respiration can be seen, similar alveolar concentrations typically being attainable at a half-stop lower vaporizer setting.

Nitrogen concentrations within the circuit increased to a peak over the first few minutes, and maximum values of 25–56% were seen.

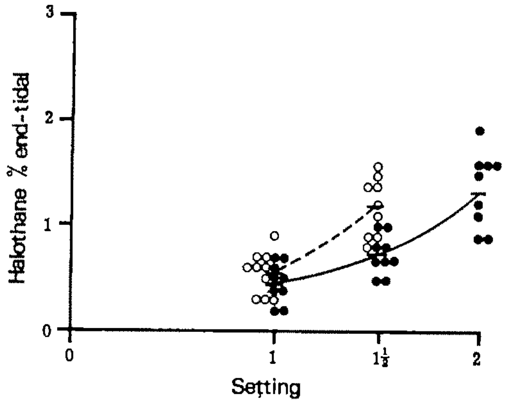

FIG. 5. End-tidal halothane concentrations. Data for spontaneous respiration based on nine patients only. (For legend see figure 3.)

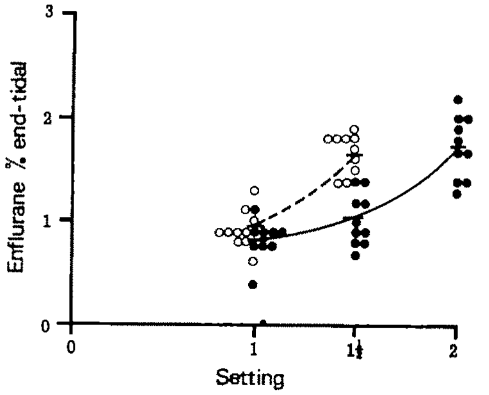

FIG. 6. End-tidal enflurane concentrations. Data from 10 patients. (For legend see figure 3.)

DISCUSSION

Inspired concentrations of halothane developed during spontaneous respiration agreed with previous work on a very similar system (Bushman et al., 1977). The lower volatility of enflurane is more than outweighed by its lower blood-gas solubility coefficient and, as might be expected, in-circuit concentrations increased to greater values. Perhaps more surprising is the finding that IPPV to 5% end-tidal carbon dioxide produced only a comparatively small increase in inspired volatile concentrations, despite the fact that in some individuals ventilation to normocapnia involved a sizeable increase in alveolar ventilation. The true difference in conditions between spontaneous and controlled ventilation can only be seen when the end-tidal concentrations are examined, where the additive effects of an increase in inspired concentration and increased alveolar ventilation produce dramatic increases in alveolar volatile concentrations. Any element of hyperventilation would move the curves in figures 5 and 6 even further apart and steepen the characteristic of the curve for IPPV to a point where the scale on the vaporizer became dangerously cramped.

Nitrogen accumulation, as the tissue and FRC nitrogen emerged to dilute the contents of the circle, resulted in maximum nitrogen concentrations of more than 50% in some individuals. Preservation of even 10% nitrogen in the inspired mixture is of theoretical benefit to the patient and is to be encouraged in oxygen-filled circles. Unless the use of nitrous oxide is contemplated, then preoxygenation of the patient, or periods of high fresh gas flows before closing the circle would seem unnecessary precautions with a circuit of this volume, provided that it is flushed with oxygen first.

A considerable saving in liquid enflurane was possible, the hourly consumption being of the order of 10 ml. A non-rebreathing system supplying similar concentrations could consume 10 times this quantity.

Continuing concern about atmospheric pollution and the increasing attention directed to systems that preserve heat and humidity in inspired gas has renewed interest in closed circuits. Their safe use requires meticulous attention.

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HALOTHANE ET ENFLURANE EN CIRCUIT FERME AYANT UN VAPORISATEUR GOLDMAN INCLUS DANS LE CIRCUIT

RESUME

Un système absorbant en circuit fermé, comprenant un vaporisateur Goldman incorporé dans le circuit, a été utilisé pour administrer de l'halothane et de l'enflurane dans de l'oxygène à des patients adultes. Les concentrations d'agent volatil atteintes, inspirées et de fin d'expiration ont été mesurées par spectrométrie de masse, après une période de stabilisation à chaque réglage du vaporisateur. Pendant la respiration spontanée sous halothane les plages des concentrations inspirées aux réglages 1, 1½ et 2 ont respectivement été de 0,5–0–9%, 1,4–2,4% et 3,3–4,5%. Les concentrations correspondantes d'enflurane inspiré aux mêmes réglages ont été de 0,8–1,4%, 1,9–2,8% et 3,7–5%. L'IPPV (ventilation au moyen de respirateurs à pression positive intermittente) à 5% de gaz carbonique en fin d'expiration, bien qu'augmentant légèrement les concentrations inspirées, a produit des augmentations considérables dans les concentrations de fin d'expiration. On s'est servi d'un minimum de pré-oxygénation pour estimer le problème de l'accumulation d'azote dans le circuit. La concentration d'azote maximale a été de 56%.

HALOTHAN UND ENFLURAN IM GESCHLOSSENEN KREISLAUF UNTER ANWENDUNG EINES IM KREIS ANGESCHLOSSENEN GOLDMAN-VERDAMPFERS

ZUSAMMENFASSUNG

Ein Umlauf-Absorptionssystem mit einem im Kreis angeschlossenen Goldman-Verdampfer wurde verwendet, um Halothan oder Enfluran in Sauerstoff bei erwachsenen Patienten zu verabreichen. Die nach einer Stabilisierungsperiode bei jeder Einstellposition erreichten inspirierten und expirierten Konzentrationen des flüchtigen Mittels wurden mittels Massenspektrometrie gemessen. Die bei den Einstellpositionen 1, 1,5 und 2 während spontaner Atmung unter Halothan ermittelten inspirierten Konzentrationsbereiche waren 0,5–0,9%, 1,4–2,4% und 3,3–4,5%. Die entsprechenden inspierten Enflurankonzentrationen bei den gleichen Einstellpositionen waren 0,8–1,4%, 1,9–2,8% und 3,7–5,0%. Obwohl es die inspirierten Konzentrationen etwas steigerte, führte IPPV auf 5% expiertes Kohlendioxyd zu beträchtlichen Steigerungen der expirierten Konzentrationen. Eine minimale Voroxygenisation wurde verwendet, um die Probleme der Stickstoffanhäufung innerhalb des Systems auszuwerten. Die maximale Stickstoffkonzentration betrug 56%.

HALOTANO Y ENFLURANO EN CIRCUITO CERRADO, USANDO UN VAPORIZADOR GOLDMAN EN EL CIRCUITO

SUMARIO

Se usó un sistema absorvente en circuito cerrado, que incorporaba un vaporizador Goldman en el circuito, para administrar halotano o enflurano en oxígeno a pacientes adultos. Se emitieron para cada establecimiento del vaporizador y mediante espectrometría de masas, lás concentraciones de inspiración y de la respiración de Cheyne-Stokes terminal que se lograron, en relación a los agentes volátiles, después de un periodo de estabilización. Durante la respiración espontáneo bajo halotano, las gamas de las concentraciones inspiradas en los establecimientos 1, 1½ y 2, fueron respectivamente de 0,5–0,9%, 1,4–2,4% y de 3,3–4,5%. Las concentraciones de enflurano inspirado correspondientes a los mismos establecimientos fueron de 0,8–1,4%, 1,9–2,8% y de 3,7–5,0%. El porcentaje inspirado por volumen, hasta el 5% de dióxido de carbono, en la respiración de Cheyne-Stokes terminal, aunque incrementó ligeramente las concentraciones inspiradas, produjo incrementos considerables en las concentraciones de la respiración de Cheyne-Stokes terminal. Se usó una preoxigenación mínima para evaluar el problema de la acumulación de nitrógeno dentro del circuito. La concentración maxima de nitrógeno fue del 56%.

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ALFENTANIL–OXYGEN ANAESTHESIA FOR CORONARY ARTERY SURGERY

S. DE LANGE, T. H. STANLEY AND M. J. BOSCOE

SUMMARY

The anaesthetic properties of alfentanil were evaluated in 15 patients undergoing coronary artery bypass grafting operations. Alfentanil was infused at a rate of 3.0 mg min^{-1} until the patients (breathing pure oxygen) became unconscious. Additional alfentanil 2.5–5.0 mg i.v. was given if systolic arterial pressure increased by 15% or more from control values. Alfentanil produced unconsciousness in 75±18 s, but muscle rigidity occurred in 27% of patients. Cardiovascular dynamics were minimally altered during the induction of anaesthesia and throughout most of the operation, although 60% of patients became hypertensive during sternotomy and 73% during sternal spread. Recovery from anaesthesia was rapid with patients regaining consciousness after 1.4±0.6 h and fulfilling our criteria for extubation of the trachea 4.1±1.2 h after operation. No patient was aware of laryngoscopy, endotracheal intubation or any aspect of the operation.

Fentanyl anaesthesia is used frequently in seriously ill patients because it produces adequate anaesthesia with little or no change in cardiovascular dynamics and appears to block the metabolic and cardiovascular "stress responses" during operation (Dubois-Primo, 1975; Hall et al., 1978; Stanley and Webster, 1978; Stanley, Philbin and Coggins, 1979; Hall, 1980; Stanley et al., 1980). Unfortunately, chest wall rigidity can occur during the induction of anaesthesia with fentanyl (Hill et al., 1980; de Lange, Stanley and Boscoe 1980a) and respiratory depression persists for some hours after operation following the administration of anaesthetic doses (Stanley and Webster, 1978; Lunn et al., 1979; Stanley, Philbin and Coggins, 1979; de Lange, Stanley and Boscoe, 1980a). In this study alfentanil, (N-[1-[2-(4 ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl-ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenyl-propanamide) (fig. 1)—a new, short-acting narcotic, structurally related to fentanyl but with only one-third of its potency and duration of activity (de Castro et al., 1979)—was evaluated as the sole anaesthetic in 15 patients undergoing coronary artery bypass grafting (CABG) operations.

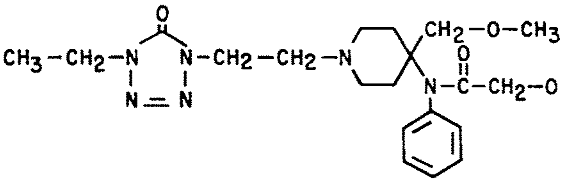

FIG. 1. Structural formula of alfentanil.

PATIENTS AND METHODS

The study was approved by the Leiden University Human Experimentation Committee and informed consent was obtained from each patient at the time of the preoperative visit (14 male patients and one female patient with multi-vessel coronary artery disease about to undergo CABG operation). Fourteen of the patients were taking propranolol or another beta-adrenergic blocking compound and 12 nitroglycerin or other oral vasodilator for hypertension or angina, or both. The patients were premedicated with lorazepam 0.08 mg kg^{-1}, by mouth 2 h before operation and atropine 0.1 mg 15 kg^{-1} i.m. 30 min before arrival in the operating room. Patients taking a beta-adrenergic blocker received their usual dose of the compound at the time of premedication.

On arrival in the operating room catheters were placed in a hand vein and a radial artery, and a bipolar lead II electrocardiogram was recorded continuously. Before the induction of anaesthesia, a thermodilution flow-directed balloon-tipped pulmonary artery catheter (Instrument Laboratories triple-lumen 110 cm model 44166 7F) was introduced percutaneously to the pulmonary

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artery through an antecubital vein using a 7-French gauge Cordis introducer.

Following preparatory procedures and a 10-min stabilization period, control measurements of the heart rate (beat min^{-1}), cardiac output (litre min^{-1}) (measured by thermodilution with 10 ml of 10–15 °C 5% dextrose in water as the injectate), systolic and mean arterial pressures (mm Hg) were obtained and patients given 100% oxygen to breathe. Two minutes later pancuronium 0.02 mg kg^{-1} was administered i.v. Three minutes after pancuronium the patients were given alfentanil 0.5 mg ml^{-1} at a rate of 3 mg min^{-1} until they became unconscious. Respirations were first spontaneous, then assisted and finally controlled, using a face-mask and a semi-closed system. Pa_{CO_2} was maintained at 4.5–5 kPa as measured in radial arterial blood every 15–45 min. During the infusion of alfentanil the patients were asked to open the eyes and take a deep breath every 5–10 s. Failure to respond to three consecutive commands was equated with unconsciousness. Once consciousness had been abolished suxamethonium 1.5 mg kg^{-1} was administered i.v., the trachea intubated with a cuffed Portex endotracheal tube and the lungs ventilated with 100% oxygen. After the onset of unconsciousness, but before intubation, additional alfentanil was given (1–2 mg i.v. bolus doses) if the patient opened the eyes, moved an extremity, or responded in any fashion which suggested that anaesthesia may not be adequate. Following intubation of the trachea and throughout operation, alfentanil was given i.v. in bolus doses of 2.5–5.0 mg whenever systolic arterial pressure increased by more than 15% of its preanaesthetic (control) value. When three successive supplementary doses of the drug failed to decrease systolic arterial pressure to within 15% of the preanaesthetic value before or during cardiopulmonary bypass, the patients were given phentolamine in 1–3 mg divided doses until arterial pressure decreased to control. After bypass 50% nitrous oxide in oxygen was added to the mixture of gases to treat hypertension not responding to supplementary doses of alfentanil. If nitrous oxide was ineffective in decreasing post-bypass hypertension to within 15% of control systolic arterial pressure, an infusion of sodium nitroprusside 0.5–2.0 µg kg^{-1} min^{-1} was started. The frequency of increases in systolic arterial pressure to more than 20% of the preanaesthetic values during endotracheal intubation, chest incision, sternotomy and maximum sternal spread was recorded.

Neuromuscular blockade was induced with pancuronium 0.08 mg kg^{-1} slowly, i.v. 15-20 min after the induction of anaesthesia and maintained with 0.02–0.04 mg kg^{-1} increments of pancuronium every 45–60 min throughout the remainder of the operation. A balanced solution of 4.5% glucose in 0.1% physiological saline was administered at a rate of 1 litre h^{-1} during the preparations before anaesthesia and 200-250 ml h^{-1} for the duration of the operative procedure. Whole blood was given after cardiopulmonary bypass and in the period after operation to maintain right atrial pressure at preanaesthetic values. The extracorporeal system was primed with Ringer's solution 1500 ml, glucose 5% in water 500 ml and 500 ml of a solution containing albumin 100 g and heparin 500 unit. Patients were cooled to 26–28 °C during extracorporeal support and rewarmed to 37 °C at its conclusion.

Cardiovascular dynamics were recorded before the induction of anaesthesia (control), at the onset of unconsciousness, 1 min after intubation, immediately before and 5 min after chest incision, before sternotomy and 5 and 10 min after sternal spread.

The presence of muscle rigidity during induction was evaluated by the following scoring system: none = no difficulty with ventilation during manual positive pressure ventilation and no clinical evidence of abdominal wall (palpation) or upper limb stiffness (manual elbow flexion); mild = possible to ventilate, but with some difficulty associated with mild abdominal wall upper stiffness or both; severe = virtually impossible to ventilate before administration of suxamethonium associated with marked abdominal wall, face, neck, and upper limb muscle stiffness.

The lungs were ventilated mechanically until the morning after surgery. During the first 8 h after operation the possibility of return of consciousness was assessed every 15 min. Patients were considered conscious when they could give correct response to three consecutive questions. Once conscious, the ability to sustain adequate spontaneous ventilation was determined every 30 min. Patients were not considered ready for possible extubation of the trachea until they had a period of stable cardiovascular measurements for 2 h. Following this, extubation was considered possible if patients could maintain a spontaneous respiratory rate of at least 8–10 b.p.m., could generate a negative inspiratory pressure of 20 mm Hg and could sustain Pa_{CO_2} of less than 6 kPa and a Pa_{O_2} of 13 kPa or more while breathing spontaneously (without encouragement) 40% oxygen via a T-piece apparatus for 20 min. The trachea was not extubated until the morning after surgery because of intensive care unit practice. To facilitate mechanical ventilation after our test period, sedatives or analgesics were administered throughout the night as deemed necessary. All patients were interviewed 48 h after operation. Questions were specifically directed at determining the presence or absence of pain and memory of laryngoscopy, endotracheal intubation and any aspect of the operative procedure.

Data were analysed for statistical significance using Student's paired *t* test.

RESULTS

The patients' mean age was 56±6 yr (range 44–63 yr) and mean weight 81±9 kg (range 60–98 kg). Unconsciousness was produced with an average of alfentanil 3.8±0.9 mg (46 μg kg^{-1}) in 75±18 s (fig. 2). However, additional alfentanil was required for intubation in 80% of patients and by the time of incision the total dose of alfentanil given was almost 10 times the induction dose. It was necessary to administer alfentanil throughout the operation to keep patients adequately anaesthetized and to maintain arterial pressures within 15% of preanaesthetic (control) values. An average of alfentanil 99±9 mg or 1.22±0.02 mg kg^{-1} was required for the entire operation (fig. 2).

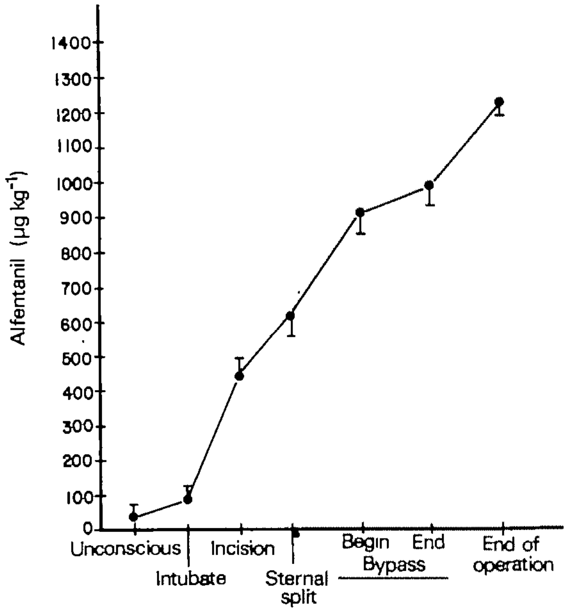

FIG. 2. Cumulative doses of alfentanil administered to 15 patients undergoing coronary artery bypass operations.

Muscle rigidity occurred in four patients (27%). However, in only one patient was rigidity so severe that positive pressure ventilation was impossible without suxamethonium. The induction of anaesthesia with alfentanil produced small but significant decreases in systolic and mean arterial pressure but did not significantly change any other variable measured (table I). The changes in systolic and mean arterial pressures were transient and all pressures were similar to control at the time of incision. Heart rate, cardiac output and mean pulmonary artery pressure remained unaltered throughout the entire study. Arterial pressures were not significantly changed before cardiopulmonary bypass with the exception of 10 min following maximal sternal spread when they, and right atrial pressures, were significantly increased. These increases responded rapidly to additional alfentanil so that phentolamine was never required before bypass (table II). However, increases in arterial pressure occurred suddenly and were often dramatic with stressful stimulation (sternotomy and sternal spread). As a result, although arterial pressures were not significantly increased 5 min after sternal spread, and only slightly increased 5 min later, 60% of patients had transient increases in systolic arterial pressure greater than 25% following sternotomy and 73% following maximal sternal spread (table III). Phentolamine was required to control arterial pressure in four patients (27%) during bypass. Forty-seven per cent of patients received nitrous oxide and 33% nitroprusside in addition after cardiopulmonary bypass to control arterial pressure. All patients but one were conscious within 3 h of the end of operation and fulfilled the criteria for endotracheal extubation within 5 h: consciousness returned, on average, 1.4±0.6 h after operation and patients fulfilled the criteria for extubation after 4.1±1.2 h in the intensive care unit.

When interviewed after operation no patient remembered laryngoscopy, endotracheal intubation or any aspect of the anaesthetic or surgical procedure.

TABLE I. *Cardiovascular responses during anaesthesia and operation (mean ± SD). *P < 0.05, Student's paired t test compared with control*

				Incision			After sternal spread	
	Control	Unconscious	Intubation	Before	5 min	Before sternotomy	5 min	10 min
Heart rate (beat min^{-1})	69	61	65	66	62	61	62	65
	±8	±7	±8	±9	±7	±9	±9	±7
Cardiac output (litre min^{-1})	6.0	5.8	5.6	6.1	5.8	5.7	6.1	6.3
	±0.7	±0.5	±0.9	±0.8	±0.9	±1.0	±1.1	±1.0
Systolic arterial pressure (mm Hg)	130	115*	120	126	125	134	139	144*
	±11	±10	±12	±13	±10	±14	±13	±12
Mean arterial pressure (mm Hg)	88	78*	82	83	85	94	95	97*
	±7	±6	±7	±8	±7	±9	±9	±8
Mean right atrial pressure (mm Hg)	6	7	8	7	8	8	9	10*
	±2	±2	±2	±2	±2	±2	±3	±2
Mean pulmonary artery pressure (mm Hg)	17	20	20	18	18	20	19	18
	±3	±3	±3	±3	±3	±3	±4	±3

TABLE II. *Per cent of patients requiring supplementation with phentolamine, nitrous oxide or nitroprusside during CABG operations with alfentanil–oxygen anaesthesia*

Phentolamine			
Before (%)	During bypass (%)	Nitrous oxide after bypass (%)	Nitroprusside after bypass (%)
0	27	47	33

TABLE III. *Per cent of patients with increases in systolic arterial pressure greater than 20% of control values during CABG operations with alfentanil–oxygen anaesthesia*

Intubation (%)	Incision (%)	Sternotomy (%)	Sternal spread (%)
0	0	60	73

DISCUSSION

This study demonstrated that large doses of alfentanil, like equivalent doses of fentanyl, produce unconsciousness with little change in cardiovascular dynamics. The data suggest that, when compared with fentanyl–oxygen anaesthesia in a similar group of patients from a similar population (de Lange, Stanley and Boscoe, 1980a), the induction of anaesthesia and recovery from anaesthesia are more rapid with alfentanil, but the frequency of muscle rigidity at induction is similar and systemic hypertension during severe surgical stress is more common.

Recent work has confirmed the cardiovascular stability originally described by Stanley and co-workers (Stanley and Webster, 1978; Lunn et al., 1979; Stanley, Philbin and Coggins, 1979) with high-dose fentanyl–oxygen anaesthesia (Hill et al., 1980; de Lange, Stanley and Boscoe, 1980a, b; Waller, Hug and Nagle, 1981) but has also suggested that muscle rigidity, intra-operative hypertension and prolonged respiratory depression after operation are occasional problems associated with this technique. The frequency of these problems appears to be related to the total dose and rate of infusion of fentanyl, the time of administration of the neuromuscular blocker, population differences, prior drug therapy and experience with the technique (de Castro, 1976; Hill et al., 1980; de Lange, Stanley and Boscoe, 1980a, b).

We have found that by using lorazepam 0.08 mg kg^{-1} orally as premedication, and by pretreating patients with pancuronium 0.02 mg kg^{-1}, i.v. before anaesthesia, muscle rigidity during the induction of anaesthesia with fentanyl at an infusion rate of 400 µg min^{-1} was decreased to approximately 10–20% (de Lange, Stanley and Boscoe, 1980a, b). At this infusion rate unconsciousness occurs in 4–5 min (de Lange, Stanley and Boscoe, 1980a). It is possible to decrease the duration of induction by infusing the fentanyl more rapidly or by using a bolus of at least 50 µg kg^{-1}. However, the frequency of muscle rigidity increases significantly and bradycardia and hypotension may occur (Hill et al., 1980; de Lange and Stanley, unpublished observations). Other workers have attempted to expedite induction and minimize rigidity by administering a full neuromuscular blocking dose of pancuronium with a large bolus of fentanyl (Bovill and Sebel, 1980; Hill et al., 1980; Waller et al., 1981). Although this technique prevents rigidity, hypotension and bradycardia, it may induce tachycardia and hypertension instead (Waller et al., 1981).

It was hoped that, when compared with fentanyl, alfentanil would maintain cardiovascular stability, decrease the duration of induction and recovery and decrease the frequency of muscle rigidity. In animals equipotent doses of alfentanil have little effect on cardiovascular dynamics, result in shorter onset and recovery times and possess a greater $ED_{50}:LD_{50}$ ratio than fentanyl (de Castro et al., 1979; C. Niemeggers, unpublished data). Although anaesthesia was induced in approximately 75 s with alfentanil 3.0 mg min^{-1} in this study, this resulted in a 27% frequency of muscle rigidity. Rapid administration of a 10-mg bolus of alfentanil and a full neuromuscular blocking dose of pancuronium resulted in a more rapid induction of anaesthesia than observed in this study without evidence of rigidity, but was likely to produce tachycardia or hypertension, or both (de Castro et al., 1979).

Increase in systolic arterial pressure of 20% or more occurred in 60% of our patients during sternotomy and in 73% during sternal spread. This was significantly greater than occurred in similar patients anaesthetized with large doses of fentanyl and oxygen (de Lange, Stanley and Boscoe, 1980a). However, most of the hypertensive episodes in this study responded quickly to additional alfentanil. As a result, the need for supplements (phentolamine, nitrous oxide, sodium nitroprusside) before, during and after bypass was not significantly different than we have reported during high-dose fentanyl anaesthesia (de Lange, Stanley and Boscoe, 1980a). However, need for these supplements, which we regard as an undesirable feature of narcotic-oxygen anaesthetic techniques, was still greater than with sufentanil-oxygen anaesthesia (de Lange, Stanley and Boscoe, 1980a).

Problems with hypertension during coronary artery surgery with alfentanil-oxygen anaesthesia may have occurred because of the extremely short duration of action of alfentanil. This suggests that the frequency of intraoperative hypertension may be decreased or perhaps even eliminated by the administration of a continuous infusion of the compound.

Return of consciousness occurred approximately 1 h after the end of operation. Patients fulfilled our criteria for possible extubation approximately 3 h later. These time are significantly shorter than were noted in similar patients anaesthetized with fentanyl or sufentanil and oxygen (Lunn et al., 1979; Stanley, Philbin and Coggins, 1979; de Lange, Stanley and Boscoe, 1980a, b). Speedy recovery after even large doses of alfentanil is probably related to rapid dissociation of the compound from central nervous system opiate receptors (J. Leysen, personal communication). The dissociation constant of alfentanil from rat brain opiate receptors is significantly lower than fentanyl or any other natural or synthetic narcotic currently available (J. Leysen, unpublished observations).

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ANESTHESIE A L'AIDE D'ALFENTANIL-OXYGENE POUR LA CHIRURGIE DE L'ARTERE CORONAIRE

RESUME

Nous avons évalué les propriétés anesthésiantes de l'alfentanil sur 15 patients subissant des opérations de greffe pour une dérivation de l'artère coronaire. L'alfentanil a été injecté lentement, à la cadence de 3 mg min^{-1}, jusqu'à ce que les patients (qui respiraient de l'oxygène pur) perdent connaissance. On leur a administré par voie intraveineuse un supplément d'alfentanil 2,4–5 mg lorsque la pression artérielle systolique a augmenté de 15% ou plus par rapport aux valeurs témoins. L'alfentanil a provoqué la perte de connaissance en 75 ± 18 s, mais une rigidité des muscles s'est produite chez 27% des patients. La dynamique cardiovasculaire s'est très légèrement modifiée pendant l'induction de l'anesthésie et pendant presque toute la durée de l'opération, bien que 60% des patients soient devenus hypertensifs pendant l'incision du sternum et 73% pendant l'extension sternale. La reprise de conscience après l'anesthésie a été rapide, les patients retrouvant leurs esprits 1,4 ± 0,6 h après et satisfaisant à nos critères de détubage de la trachée 4,1 ± 1,2 h après l'opération. Aucun patient ne s'est rendu compte de la laryngoscopie, du tubage trachéal ou de tout autre aspect de l'intervention chirurgicale.

ALFENTANIL-SAUERSTOFF-ANÄSTHESIE BEI HERZKRANZARTERIENCHIRURGIE

ZUSSAMENFASSUNG

Die Anästhesie-Eigenschaften von Alfentanil wurden bei 15 Patienten ausgewertet, die Herzkranzarterienchirurgie unterzogen. Alfentanil wurde mit 3,0 mg min^{-1} eingeflösst, bis die Patienten (die reinen Sauerstoff einatmeten) bewusstlos wurden. Zusätzliches Alfentanil 2,4–5,0 mg wurde verabreicht, der systolische Arteriendruck nahm um 15% oder mehr im Vergleich zu den Kontrollwerten zu. Alfentanil führte innerhalb 75 ± 18 s zu Bewusstlosigkeit, aber Muskelstarre stellte sich bei 27% der Patienten ein. Die kardiovasculäre Dynamik änderte sich minimal während der Einleitung der Anästhesie und zum grössten Teil auch während der Operation, obwohl bei 60% der Patienten während der Brustbeinspaltung und 73% der Patienten während Sternalspreizen eine Hypertonie sich einstellte. Die Erholung von der Anästhesie ging schnell vor sich und Patienten kamen wieder nach 1,4 ± 0,6 h zum Bewusstsein und erfüllten unsere Kriterien für Trachealextubation 4,1 ± 1,2 h nach der Operation. Kein Patient war sich der Laryngoskopie, Endotrachealintubation oder irgend eines Teils der Operation bewusst.

ANESTESIA DE OXIGENO Y ALFENTANILO PARA LA INTERVENCION QUIRURJICA EN LA ARTERIA CORONARIA

SUMARIO

Se evaluaron las propiedades anestésicas del alfentanilo en 15 pacientes sometidos a intervención quirúrjica de injerto de desviación de la arteria coronaria. El alfentanilo se inyectó a un ritmo de 3,0 mg min^{-1} hasta que los pacientes (que respiraban oxígeno puro) quedaron anestesiados. Se administraron cantidades complementarias de alfentanilo, de 2,4 a 5,0 mg, si la presión sistólica arterial incrementaba en un 15%, o valor superior, con respecto a los valores de control. El alfetanilo produjo inconsciencia en un 75 ± 18 por ciento de los pacientes, presentándose rigidez muscular en un 27% de éstos. Las características dinámicas cardiovasculares quedaron mínimamente alteradas durante la inducción de la anestesia y durante la mayoría de las operaciones, aunque el 60% de los pacientes sufrieron hipertensión durante la esternotomía y el 73% durante la apertura esternal. La recuperación de la anestesia fue rápida, recuperando los pacientes el estado consciente después de 1,4 ± 0,6 h y satisfaciendo nuestro criterio para la extubación de la tráquea a las 4,1 ± 1,2 h de efectuada la operación. Ningún paciente fue consciente de la laringoscopia, entubación endotraqueal, ni de ningún otro aspecto de la operación.

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PAIN RELIEF FOLLOWING POST-GANGLIONIC SYMPATHETIC BLOCKADE WITH I.V. GUANETHIDINE

C. J. GLYNN, R. W. BASEDOW AND J. A. WALSH

SUMMARY

Thirty-one patients with pain in one or both hands associated with sympathetic dystrophy or Raynaud's disease were studied before and after the administration of a placebo and guanethidine 10 mg i.v. Before and after the injections each patient reported his pain and had sympathetic activity assessed by: (1) palmar sweating; (2) skin temperature; (3) hand blood flow and (4) the ice response of hand blood flow. There was no significant change in any index after the placebo injection, nor was there any change in palmar sweating after guanethidine. Following guanethidine there were significant changes in reported pain ($P<0.001$), skin temperature ($P<0.05$), hand blood flow ($P<0.001$) and the ice response of hand blood flow ($P<0.001$). The results confirm the importance of the post-ganglionic sympathetic nervous system in the transmission of pain in these patients.

The sympathetic nervous system is, by definition, efferent (Johnson and Spalding, 1974) and so the mechanisms by which sympathectomy relieves pain are speculative. For example, blockade of the paravertebral sympathetic ganglia by local anaesthesia, or destruction by chemical corrosives (phenol) or surgery relieves the rest pain associated with peripheral vascular disease (Barcroft and Swan, 1953) or the pain of sympathetic dystrophy (Bonica, 1980). There are many proposed mechanisms suggested to explain this association (Bonica, 1980) and these can be broadly divided into three:

Peripheral mechanisms

The suggestion that there is an abnormal connection between the sympathetic and the somatic nervous systems in causalgia (Doupe, Cullen and Chance, 1944) which explains the sympathetic component of the pain.

Spinal mechanisms

The neuronal "turbulence" hypothesis proposed by Sunderland (1976) to explain the involvement of the sympathetic nervous system in the perception of pain.

Central mechanisms

The pattern-generating mechanisms proposed by Melzack and Loeser (1978) to explain deafferentation pain which is sometimes relieved by sympathetomy.

All of these mechanisms involve conduction in the sympathetic nervous system, whereas the increase in blood flow which follows successful sympathectomy is thought to be the reason for pain relief in occlusive vascular disease (Barcroft and Swan, 1953). Apart from occlusive vascular disease and vasospastic disorders, there is no evidence to show if the mechanism of pain relief is the sympathetic blockade *per se* or the results of the sympathetic blockade (increase in blood flow, decreased sweating or increased temperature). This study was designed to investigate the relationship between reported pain and sympathetic activity in the hands of patients with sympathetic dystrophy and Raynaud's disease. The patients were studied before and after post-ganglionic sympathetic blockade with guanethidine.

PATIENTS AND METHODS

Patients

Patients presenting to the pain unit with pain in the hand or hands in association with sympathetic dystrophy or Raynaud's disease were invited to participate in the study. Informed consent was obtained from these patients to study pain and sympathetic activity before and after the i.v. injection of 10 ml of physiological saline and

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before and after 10 ml of physiological saline with guanethidine 10 mg. The patients were informed that one solution to be injected was inactive, but were not aware which solution was the placebo. The study involved 31 patients (13 male and 18 female) with a mean age of 40 yr (range 18–77 yr). Twenty-eight had a presumptive diagnosis of sympathetic dystrophy and three had Raynaud's disease. Sympathetic dystrophy (Bonica, 1980) was the diagnosis in those patients who had any four of the seven symptoms or signs shown in table I. This diagnosis was confirmed by pain relief after sympathetic blockade. Raynaud's disease is defined as intermittent pallor or cyanosis of the fingers or hands and fingers precipitated by cold or by emotional factors (Raynaud, 1862).

TABLE I. *Symptoms and signs of sympathetic dystrophy*

(1) Persistent pain—generally in a median or ulnar nerve distribution
(2) Hyperaesthesia—in a similar distribution
(3) Oedema
(4) Hyperhydrosis
(5) Colour changes—cyanosis or pallor
(6) Radiographic evidence of bone demineralization (Sudeck's atrophy)
(7) A history of injury

Procedure

The technique used was the Hannington-Kiff (1974) modification of the Bier block (1908) which meant that during these injections the treated hand was isolated from the rest of the body by a tourniquet around the arm inflated to more than systolic arterial pressure. The study was conducted in a quiet, dimly lit, air-conditioned laboratory (21 ± 0.5 °C). Auditory stimuli were excluded by playing a tape of background music selected by the patient, through headphones.

Pain was reported by the patient using the visual analogue scale (Ohnaus and Adler, 1975). Sympathetic activity was assessed by (1) palmar sweating, measured by using the cobalt blue sweat test (Cousins et al., 1979); (2) skin temperature, measured by a thermistor (Yellow springs) placed on the anterior aspect of the wrist; (3) hand blood flow, measured in a water-filled plethysmograph at 34 ± 1 °C by venous occlusion plethysmography (Greenfield, 1954); (4) the ice response of hand blood flow, also measured by venous occlusion plethysmography (Jamieson, Ludbrook and Wilson, 1971). This measurement period was approximately 1 h. This order was maintained throughout the study.

I.v. cannulae were placed in both cubital fossae. A tourniquet around the affected arm was inflated to 300 mm Hg and physiological saline 10 ml injected i.v. The tourniquet was maintained at greater than the patient's systolic arterial pressure for 10 min and then released slowly over 5 min.

Pain and sympathetic activity were again assessed and this took approximately 1 h. The tourniquet was inflated to 300 mm Hg once again and guanethidine 10 mg in physiological saline 10 ml injected i.v. The tourniquet was released as described previously. Pain and sympathetic activity were assessed. Reported pain and sympathetic activity were assessed again 7 days later in 28 of the 31 patients. During and after the studies the patients were encouraged to report any complaints or problems.

Statistical analysis

The results were analysed with the non-parametric Wilcoxon two-tailed *t* test. The results obtained at each measurement period from the treated and untreated (control) hands were compared. Comparisons were made between the baseline results and those obtained after saline and after guanethidine in both treated and untreated hands. In addition, the results obtained after saline in both treated and untreated hands were compared with those obtained after guanethidine in both treated and untreated hands.

Results were "normalized" to overcome any effects of spontaneous variations in the control (untreated) hand. The ratio of the results of skin temperature and hand blood flow from the treated and untreated hands after guanethidine were compared with those ratios obtained at baseline and after saline. The difference was used instead of the ratio when comparing the ice response before and after each procedure because the ice response was already expressed as a percentage. Reported pain was the only exception to this and was reported globally before and after each injection.

RESULTS

Pain (table II)

There was a significant difference between the reported pain score (cm) obtained after guanethidine compared with the baseline results ($P < 0.001$). In addition there was a significant difference between the post-guanethidine results

TABLE II. *Pain score (cm) (mean ± SD).* ***P < *0.001 cf. baseline;* *P < *0.05 cf. after saline*

Baseline	3.4±3.2
After saline	2.1±2.8
After guanethidine	***0.9±1.5***
7 days later	2.7±3.1

Tables II–V: The non-parametric Wilcoxon two-tailed *t* test was used in the statistical analyses. Normalized data are the ratio of the treated results to the untreated results in respect to temperature and hand blood flow. The ice response of hand blood flow is expressed as a percentage decrease in flow. Thus the normalized data are the difference between the treated and untreated results.

and those following saline ($P < 0.05$), but no significant difference was found when the baseline and post-saline results were compared.

Palmar sweating

There was no significant change when comparisons were made between any of the measurements of palmar sweating (% change).

Skin temperature (table III)

The only significant change found in skin temperature (°C) was when the post-guanethidine results were compared with the baseline results ($P < 0.05$).

TABLE III. *Temperature (°C) (mean ± SD).* *P < *0.05 cf. baseline*

	Treated hand	Untreated hand	Normalized data
Baseline	30.5±2.3	30.9±2.2	0.9±0.03
After saline	30.9±1.7	31.1±1.6	0.9±0.04
After guanethidine	31.4±1.6*	31.2±2.1	0.9±0.06
7 days later	31.1±2.1	31.2±1.9	1.0±0.04

Hand blood flow (table IV)

After guanethidine, a significant increase in hand blood flow (ml min^{-1} per 100 ml of tissue) was found when the treated and untreated hands were compared ($P < 0.001$). There were also significant increases in hand blood flow when the baseline results were compared with the post-guanethidine results ($P < 0.001$) and also when the post-saline results were compared with those obtained after guanethidine ($P < 0.02$). In addition, when the ratios between the treated and untreated hands after guanethidine were compared with those obtained at baseline and after saline the differences were found to be statistically significant ($P < 0.002$ and $P < 0.05$ respectively). There was no significant difference in hand blood flow found in any of the comparisons of baseline and post-saline results and there were no significant differences when the untreated hands were compared.

TABLE IV. *Hand blood flow (ml min^{-1} per 100 ml tissue) (mean ± SD).* *P < *0.05 cf. after saline;* **P < *0.01 cf. baseline;* ***P < *0.001 cf. untreated and baseline;* †P < *0.02 cf. after saline;* ‡P < *0.002 cf. baseline*

	Treated hand	Untreated hand	Normalized data
Baseline	6.8±5.4	6.0±4.4	1.2±0.5
After saline	6.6±5.6	5.6±4.1	1.2±0.6
After guanethidine	8.3±5.6†***	5.6±4.2	1.8±1.5*‡
7 days later	7.3±6.1	7.8±6.3	0.9±0.3**

Ice response of hand blood flow (table V)

There was a significant change ($P < 0.002$) in the ice response (% decrement) when the treated and untreated hands were compared following guanethidine. There were also significant changes when the post-guanethidine results in the treated hands were compared with the baseline ($P < 0.001$) and post-saline ($P < 0.001$) results. When the difference found in the ice response between treated and untreated hands was compared with that found at baseline and after saline, a statistical significance of $P < 0.02$ for both was found. In addition, when the results in the untreated hands after guanethidine were compared with those obtained at baseline and after saline the difference was statistically significant ($P < 0.02$) for both.

TABLE V. *Ice response (% decrement) (mean ± SD).* **P < *0.01 cf. untreated;* ***P < *0.001 cf. baseline and after saline;* †P < *0.02 cf. baseline and after saline;* ‡P < *0.002 cf. untreated after guanethidine*

	Treated hand	Untreated hand	Normalized data
Baseline	37±25	40±22	−3±16
After saline	37±26	40±22	−3±22
After guanethidine	18±21***‡	31±24†	−13±26†
7 days later	35±27**	43±25	−8±17

There were no reports of untoward effects of either treatment from any patient, in particular there were no symptoms nor signs of somatic nerve blockade.

7-Day follow-up

On the 7-day assessment no significant differences were found in any of the comparisons involving pain, palmar sweating and skin temperature. However with hand blood flow there was a significant difference ($P < 0.01$) when the baseline ratio was compared with that found at 7 days, but no other significant change. A significant difference ($P < 0.01$) in the ice response was found when treated and untreated hands were compared at the 7-day assessment.

DISCUSSION

The significant decrease in reported pain ($P < 0.001$) following i.v. guanethidine in conjunction with the blockade of sympathetic activity confirms the importance of the sympathetic nervous system in the transmission of pain in these patients. The action of guanethidine is on the post-ganglionic sympathetic nervous system where it displaces noradrenaline from the presynaptic vesicles and prevents reuptake of noradrenaline and, in addition, blocks the release of the catecholamines normally produced by nerve stimulation (Woosley and Nies, 1976). Thus, whatever the relationship between the sympathetic nervous system and the transmission of pain, the post-ganglionic synapse appears to be intimately involved. There was no evidence of somatic neural blockade following i.v. guanethidine, suggesting that the pain relief was not a result of a direct effect of guanethidine on the peripheral somatic nervous system similar to that found by Loh and colleagues (1980). Guanethidine significantly changes afferent activity, that is pain ($P < 0.001$) as well as efferent activity, that is the ice response of hand blood flow ($P < 0.001$).

Palmar sweating and skin temperature

Palmar sweating is mediated by acetylcholine at the post-ganglionic synapse in the hands (Johnson and Spalding, 1974) and so the absence of any change was not unexpected. The significant increase in skin temperature ($P < 0.05$) in the treated hand following guanethidine may be an artefact, in that during each study period of approximately 1 h, the hands were warmed in the plethysmograph to 34 ± 1 °C. There was a consistent increase in temperature in both hands from the first to the third measurement (table III).

Hand blood flow

All the comparisons of hand blood flow involving the treated hand after guanethidine revealed significant differences (table IV), whereas no significant changes were found when the untreated hands were compared, nor were there any significant changes found in either hand when comparisons were made between the baseline results and those following saline.

The significant difference ($P < 0.01$) found when the ratio of hand blood flow at baseline was compared with the ratio at 7 days is a consequence of the fact that the blood flow in the untreated hand was greater than that in the treated hand at 7 days. There are two possible explanations for this. The first and most likely explanation is that there is some reflex vasodilatation of the untreated hand as a result of the pain relief or the vasodilatation, or both, of the treated hand. A second possible explanation is that there is a residual effect of the guanethidine in the untreated hand. However, the significant difference in the ice response (table V) found at the same time suggests that the guanethidine, if present, is to be found in the treated and not the untreated hand. These results underline the importance of having a control (untreated) hand to compare with the treated hand, because it is well known that in the individual patient all these measures of sympathetic activity vary from time to time as well as from day to day (Kaneko, Zechman and Smith, 1968); this variation is presumably in a similar direction in both hands at the same time.

The ice response of hand blood flow

After guanethidine significant differences were observed in the ice response in the treated hand with all comparisons, whereas there was no significant difference in either hand when the baseline and post-saline results were compared. The ablation of the ice response when the treated and untreated hands were compared 7 days later suggests that there is still some active drug in the treated hand, which is consistent with the 5-day half-life of guanethidine (Woosley and Nies, 1976). The significant difference ($P < 0.02$) in the ice response when the untreated hands after guanethidine were compared with the results at baseline and post-saline is almost certainly a result of the redistribution of guanethidine to the untreated hand after the release of the tourniquet (Glynn et al., 1981). This further suggests that the ice response of hand blood flow is the most sensitive of the battery of tests used for sympathetic activity in the study.

Whatever the mechanism underlying this relationship, it would seem to be intimately related either to the release of noradrenaline or to an effect of guanethidine itself. Guanethidine replaces noradrenaline in the symphathetic nerve endings, thus there is an initial release of noradrenaline. No patient reported any increase in pain following guanethidine, suggesting that noradrenaline itself is not the chemical instigator of the pain. This does not support Torebjork and Hallin (1980) who reported that noradrenaline injected subcutaneously into patients whose pain had been relieved by sympathectomy, reproduced the original pain. It has also been postulated that noradrenaline decreases the threshold of somatic peripheral receptors or nerves (Wall and Devor, 1978); the results from the patients studied do not support this. It is possible that guanethidine itself is providing the analgesia by a direct effect on a somatic peripheral receptors or nerves. However, both this study and that reported by Loh and colleagues (1980) found no evidence of somatic blockade.

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SOULAGEMENT DE LA DOULEUR SUIVANT BLOCAGE SYMPATHIQUE POSTGANGLIONNAIRE À L'AIDE D'UNE INJECTION INTRAVEINEUSE DE GUANÉTHIDINE

RESUME

Trente-et-un patients souffrant de douleurs, dans une main ou dans les deux mains, associées à la dystrophie sympathique ou syndrome de Raynaud, ont fait l'objet d'une étude avant et après l'administration d'un placébo et de 10 mg de guanéthidine par injection intraveineuse. Avant et après l'injection chaque patient a expliqué la douleur qu'il ressentait et on a évalué son activité sympathique par: (1) la transpiration des paumes; (2) la température de la peau; (3) l'écoulement du sang dans les mains et (4) la réaction à la glace de l'écoulement du sang dans les mains. Il n'y a eu de changement significatif dans aucun index après l'injection de placébo, et il n'y a eu aucun changement dans la transpiration des paumes après l'injection

de guanéthidine. Mais après l'injection de guanéthidine, il y a eu des changements significatifs dans la douleur signalée ($P<0,001$), dans la température de la peau ($P<0,05$), dans l'écoulement du sang dans les mains ($P<0,001$) et dans la réaction à la glace de l'écoulement du sang dans les mains ($P<0,001$). Ces résultats confirment l'importance du système nerveux sympathique postganglionnaire dans la transmission de la douleur chez ces patients.

SCHMERZUNDERUNG NACH RETROGANGLIONÄRER SYMPATHISCHE VERABREICHTEN GUANETHIDINS

ZUSAMMENFASSUNG

Einunddreissig Patienten mit Schmerzen in einer oder beiden Händen im Zusammenhang mit sympathischer Dystrophie oder Raynaud'scher Krankheit wurden vor und nach der Verabreichung eines Suggestionsmittels und intravenösen Guanethidins 10 mg studiert. Jeder Patient berichtete über seine Schmerzen vor und nach den Injektionen und seine sympathische Tätigkeit wurde durch (1) palmaren Schweiss (2) Hauttemperatur (3) Blutkreislauf in der Hand und (4) Reaktion des Handblutkreislaufs auf Eis ausgewertet. Nach Injizierung des Suggestionsmittels stellten sich keine bedeutende Änderungen der genannten Indizien ein, noch stellte sich eine Änderung des palmaren Schweisses nach Guanethidin ein. Nach Verabreichung von Guanethidin gab es bedeutende Änderungen der berichteten Schmerzen ($P<0,001$), der Hauttemperatur ($P<0,05$), des Handblutkreislaufes ($P<0,001$) und der Reaktion des Handblutkreislaufes auf Eis ($P<0,001$). Die Ergebnisse bestätigen die Bedeutung des retroganglionären sympathischen Nervensystems für die Übertragung von Schmerzen bei diesen Patienten.

ALIVIO DE DOLOR TRAS BLOQUEO POSGANGLIONICO SIMPATICO MEDIANTE GUANETIDINA INTRAVENOSA

SUMARIO

Antes y después de la administración de un placebo y de 10 mg de guanetidina intravenosa se efectuaron estudios en treinta y un pacientes que presentaban dolor en una mano, o en las dos, asociado con distrofia simpática o con la enfermedad de Raynaud. Antes y después de las inyecciones, cada uno de los pacientes informó de su dolor y se le evaluó la actividad simpática mediante: (1) sudor en la palma de la mano; (2) temperatura de la piel; (3) flujo sanguíneo en la mano (4) la respuesta al hielo por parte del flujo sanguíneo de la mano. No hubo ningún cambio en ninguno de los índices después de la inyección del placebo, ni tampoco hubo cambio alguno en el sudor de la mano después de la guanetidina. A raíz de la inyección de esta última, hubo un cambio significativo en el dolor informado ($P<0,001$), en la temperatura de la piel ($P<0,05$), en el flujo sanguíneo de la mano ($P<0,001$) y en la respuesta de dicho flujo al hielo ($P<0,001$). Los resultados confirman la importancia del sistema nervioso posgangliónico simpático en la transmisión de dolor en estos pacientes.

Br. J. Anaesth. (1981), 53, 1303

RECOVERY FROM PANCURONIUM BLOCKADE IN THE NEONATAL INTENSIVE CARE UNIT

N. G. GOUDSOUZIAN, R. K. CRONE AND I. D. TODRES

SUMMARY

Neuromuscular blockade with pancuronium and its antagonism was evaluated in 33 critically ill infants. The evoked contraction of the adductor pollicis from indirect stimulation of the ulnar nerve was measured. The neuromuscular blockade recovered spontaneously from pancuronium in seven infants, 23 required one or more doses of atropine 0.02 ng kg^{-1} and neostigmine 0.06 mg kg^{-1}. In three infants the blockade failed to reverse. Immature infants less than 32 weeks did not show any significant difference in their requirement for pancuronium compared with mature infants. Age and birth weight of the infant, dose of pancuronium and duration of its administration did not affect the requirements for reversal. Train-of-four and tetanus:twitch ratios were lower ($P < 0.05$) in infants less than 32 weeks of developmental age reflecting immaturity of neuromuscular transmission.

Infants with hyaline membrane disease undergoing artificial ventilation require lower peak inspiratory pressures (Stark, Bascom and Frantz, 1979) and lower inspired oxygen concentrations (Henry et al., 1979) when neuromuscular blocking agents are used. In those infants who do not develop complications, rapid improvement in lung compliance occurs approximately 72 h after birth and they no longer require neuromuscular blockade, since they can breathe spontaneously or are managed using intermittent mandatory ventilation.

Since renal function is immature, the excretion of pancuronium and its metabolites may be delayed and the frequent use of aminoglycoside antibiotics may prolong the residual neuromuscular blockade (Singh, Harvey and Marshall, 1978). The present study assessed the degree of residual neuromuscular blockade, and its reversal, in 33 critically ill infants, by measuring the evoked contraction of the adductor pollicis muscle from indirect stimulation of the ulnar nerve.

PATIENTS AND METHODS

Thirty-two infants 2–16 days and one 70 days old were studied. Their gestational age varied between 27 and 42 weeks and their weight and length of body were appropriate to their age. Their developmental age was calculated by adding the postpartum age at the time of the study to the gestational age at birth.

Each infant received intermittent doses of pancuronium 0.05 mg kg^{-1} hourly or as needed for 2–11 days as an adjunct to mechanical ventilation with the Bourne's (BP 200) time-cycled, pressure-limited respirator. Myoneural blocking agents were discontinued when arterial pressure, temperature and urine output had stabilized, and arterial blood-gas tensions indicated adequate gas exchange with FI_{O_2} greater than 0.5 at inspiratory pressures less than 28 cm H_2O. Acceptable blood-gas values were Pa_{O_2} 9 kPa or more, Pa_{CO_2} less than 5 kPa and $[H^+]$ less than 50 nmol $litre^{-1}$. Total serum calcium concentration was maintained greater than 7.5 mg dl^{-1} and gentamicin concentrations were within the therapeutic range of 1–6 μg dl^{-1}.

Neuromuscular transmission was studied with a Grass FT-03 force displacement transducer. The hand of the child was attached firmly on a padded plexiglass base with adhesive tape. The thumb was taped to a small portion of wooden tongue depressor trimmed to the size of the infant's thumb. This in turn was connected by silk thread to the force displacement transducer. The transducer was mounted on the plexiglass base with the direction of the force of concentration perpendicular to the transducer. The ulnar nerve was stimulated indirectly by surface or needle electrodes at the forearm near the wrist. The

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duration of electrical impulse was 0.2 ms (Grass S44 stimulator). The force of contraction of the thumb in response to indirect square-wave supramaximal stimuli applied at the ulnar nerve at 0.25 Hz, at 2 Hz for 2 s (train-of-four stimulation), and at 20 Hz and 50 Hz for 5 s (tetanic stimulation) was recorded on a Grass polygraph. An interval of 10 min elapsed between each tetanic stimulus to allow the twitch height to return to its normal pre-tetanic value.

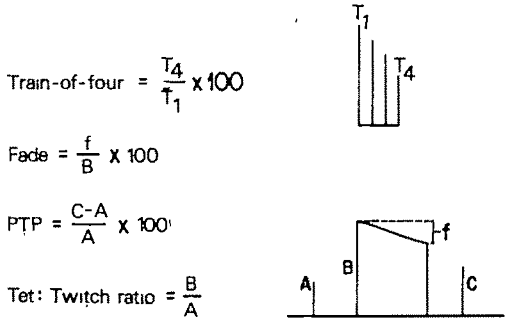
Train-of-four = $\frac{T_4}{T_1}$ x 100
Fade = $\frac{f}{B}$ x 100
PTP = $\frac{C-A}{A}$ x 100
Tet: Twitch ratio = $\frac{B}{A}$
T_1
T_4
A
B
C
f

FIG. 1. The methods used for calculation of the train-of-four, fade, post-tetanic potentiation (PTP) and the tetanus: twitch ratio.

The following data were measured from the polygraph recordings (fig. 1): (1) The train-of-four ratio: the percent ratio of the height of the fourth twitch to the first in the train-of-four stimulation at 2 Hz. (2) Tetanic fade: the percent ratio of the decrease in height of tetanic force after 5 s of stimulation of the initial force of tetanus. (3) Post-tetanic potentiation (PTP): the percentage change in the height of pre-tetanic twitch. The time interval between the end of tetanus and post-tetanic twitch was 6–8 s. (4) Tetanus: twitch ratio: the ratio of the height of tetanus to the pretetanic twitch height. (5) Tetanic heights at 20 Hz and 50Hz: the height of tetanus at 20 Hz was compared with the height of tetanus at 50 Hz.

Neuromuscular blockade was considered adequately reversed when all of the following criteria were satisfied: train-of-four greater than 80%; fade less than 30%; tetanus (at 50 Hz): twitch ratio greater than 2.

These values were based on our previous studies in infants and children anaesthetized with halothane (Goudsouzian, 1980).

If the criteria for adequacy of reversal were not met, the infant was given atropine 0.02 ng kg^{-1} and neostigmine 0.06 mg kg^{-1} and the measurements repeated (fig. 2). If, after 20 min, these criteria were still not satisfied, the doses of atropine and neostigmine were repeated and neuromuscular function re-evaluated.

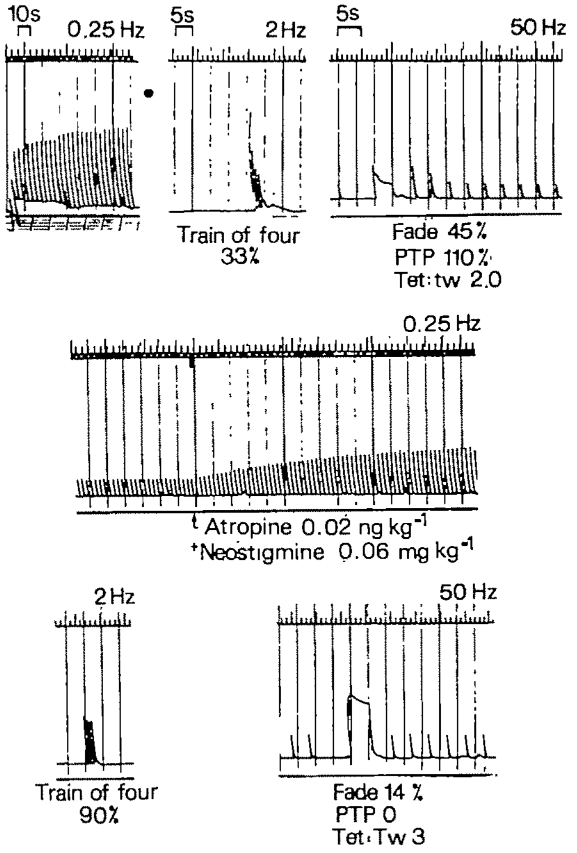

FIG. 2. A typical recording from an infant who required one dose of antagonist. Note the greater values of train-of-four and tetanus: twitch ratios and the absence of post-tetanic potentiation after reversal.

The adequacy of reversal was evaluated clinically by the presence of good muscle tone, spontaneous movements of the limbs, facial expressions, spontaneous respiratory efforts and the ability to generate 20 cm H_2O negative inspiratory pressure at the endotracheal tube.

Data were analysed by the non-correlated Student's *t* test except for comparison of tetanic heights at 20 and 50 Hz, for which the correlated *t* test was used. Differences were considered significant when *P* values were less than 0.05.

RESULTS

Thirty-three infants were studied. Three infants did not fulfil our criteria for antagonism of neuromuscular blockade after two or more attempts at reversal. Their data were excluded from the present study. Two of these three infants received the last dose of pancuronium 3 h before testing. The third infant had renal failure.

The 30 infants remaining in the study ranged from 28 to 45 weeks of developmental age and were in three groups according to age (table I). Group I were less than 32 weeks, group II were 32–38 weeks and group III were more than 38 weeks.

The average total dose of pancuronium, the number of days on which the infants received pancuronium, the average dose of pancuronium required per kg per day and the interval between the last dose and evaluation were comparable in all three groups.

A greater number of infants less than 32 weeks required two attempts at reversal (table II). In the individual infant, gestational age or post-natal age or both, birth weight, dose of pancuronium or duration of neuromuscular blockade had no predictive effect on the number of attempts required for reversal. In infants whose last dose of pancuronium was at least 20 h before testing, no pharmacological reversal of neuromuscular blockade was necessary.

We found no significant differences between fade and post-tetanic potentiation among the three groups of tested infants. The train-of-four and tetanus : twitch ratios, were less ($P < 0.05$) in group I patients when compared with groups II and III. The train-of-four, tetanic fade, post-tetanic potentiation, and tetanus : twitch ratios correlated well with adequate return of neuromuscular func-

TABLE I. *Age and birth weight of infants studied*

	Developmental age (weeks)	Gestational age (weeks)	Postnatal age (days)	Birth weight (kg)
Group I ($n = 8$)				
Mean ± SEM	30.7±0.5	30±0.6	6±1	1.6±0.1
Range	28–32	27–32	2–14	0.97–2.0
Group II ($n = 12$)				
Mean ± SEM	35.4±0.5	35±0.5	6±1	2.3±0.1
Range	33–38	32–37	3–15	1.5–2.9
Group III ($n = 10$)				
Mean ± SEM	41.4±0.7	39±0.7	17±7	3.1±0.15
Range	39–45	34–43	3–70	2.5–4.3
Mean ± SEM of three groups	36.2±0.2	34.8±1.2	9.4±4.1	2.4±0.1

TABLE II. *Doses of pancuronium administered and number of attempts at reversal. * Significant difference between the two groups* (P < *0.05*)

	Total pancuronium received (mg kg^{-1})	No. days of pancuronium (days)	Av. dose of pancuronium (mg kg^{-1} day^{-1})	Interval between last dose and evaluation (h)	Attempts at reversal
Group I					
Mean ± SEM	1.4±0.8	4.0±1.3	0.3±0.05	9±2	1.6±0.3
Range	0.05–6	1–11	0.1–0.54	4–14	1–3
					*
Group II					
Mean ± SEM	1.5±0.3	3.2±0.4	0.5±0.11	12±2	0.8±0.2
Range	0.2–3.8	2–4	0.27±1.1	4 – 26	0–2
Group III					
Mean ± SEM	1.2±0.3	3.0±0.5	0.4±0.1	9±3	0.9±0.3
Range	0.3–3.1	1–4	0.12–0.8	5–27	0–2
Mean ± SEM of three groups	1.4±0.3	3.4±0.4	0.4±0.1	10±1	1±0.1

tion as determined on clinical grounds, and with the ability to generate more than 20 cm H_2O negative intratracheal pressure. We did not observe "recurarization" in any of the infants after satisfactory reversal of neuromuscular blockade as measured by the electromechanical monitor.

The height of tetanus was greater ($P < 0.005$) at 50 Hz than at 20 Hz; the mean height at 50 Hz was 29 ± 3 mm and at 20 Hz was 24 ± 2 mm, indicating that all infants, including those born prematurely, can develop greater tension at 50 Hz than at 20 Hz.

DISCUSSION

The response of the newborn to neuromuscular blocking agents is extremely variable. Previously we described a 3.5-fold variability in the dose of neuromuscular blocking agent required to achieve 95% depression of twitch height in newborn infants (Goudsouzian et al., 1975). The infants in this present study also exhibited great variability. Their daily dose of pancuronium varied from 0.1 to 1.1 $mg\,kg^{-1}\,day^{-1}$.

The mean dose of pancuronium ($mg\,kg^{-1}\,day^{-1}$) needed for adequate neuromuscular blockade was not significantly different among the three groups of infants. This indicates the absence of any unusual sensitivity to non-depolarizing myoneural blocking agents in the immature infant (less than 32 weeks) compared with older infants. These data agree with our previous observations (Goudsouzian et al., 1975; Goudsouzian, Liu and Savarese, 1978) that neonates are not unusually sensitive to neuromuscular blocking agents, but rather, demonstrate wide variability. This observation has recently been supported by measurements of plasma concentrations of tubocurarine (Matteo et al., 1980).

In studying the reversibility of pancuronium, we noted that the neuromuscular blockade of infants who had received a large dose of pancuronium (an average 1.4 $mg\,kg^{-1}$ in 3.4 days) and aminoglycoside antibiotics could be satisfactorily reversed 10 h after the administration of the last dose. When body temperature, blood calcium concentration and blood-gas tensions are in the normal range and sufficient time has elapsed after the last dose of pancuronium (elimination segment of the pharmacokinetic curve of pancuronium (Lee and Katz, (1980)), neuromuscular blockade can be consistently reversed.

The dose of pancuronium and the number of days in which the infants received mechanical ventilation of the lungs did not have a predictable influence on reversibility. However, the degree of immaturity appeared to be a factor. Immature infants (less than 32 weeks) required more antagonist and in none was reversal spontaneous. Seven infants from the other two groups did not require any pharmacological antagonist (fig. 3). The time elapsing between the last dose of pancuronium and the number of attempts at reversal did seem to be a predictive index. The two infants in whom reversal was not adequate received their last dose of pancuronium 3 h before testing; perhaps the high plasma concentrations of pancuronium precluded reversal. Consequently, we did not attempt any pharmacological antagonism until a minimum of 4 h had elapsed after the last dose of pancuronium. The number of attempts at reversal diminished as the time elapsed increased. After 20 h, infants seem to recover spontaneously from the effect of pancuronium. None of the infants who recovered spontaneously was less than 32 weeks of developmental age (fig. 3). In addition to the time elapsing, renal excretion of pancuronium is important, as was demonstrated by the infant with renal failure who showed evidence of neuromuscular blockade 48 h after the last dose of pancuronium, despite two attempts at reversal. Renal concentrating ability is decreased in the early weeks of life (Edelmann and Spitzer, 1969). However, this factor does not seem to affect the excretion of pancuronium in neonates who have no evidence of renal failure.

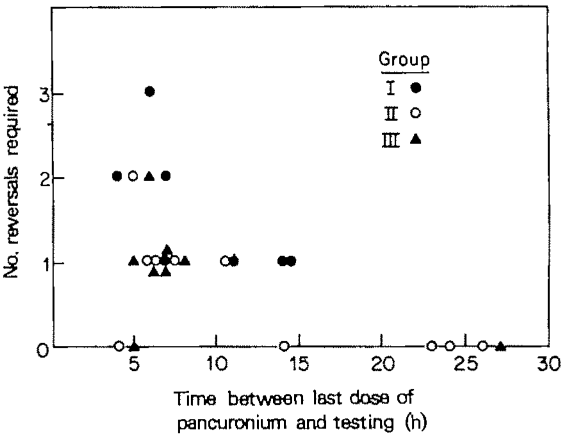

FIG. 3. The interval between the last dose of pancuronium and evaluation in the three groups of neonates studied.

One of the most important findings of the present study is that the train-of-four and the

TABLE III. *Neuromuscular indices in critically ill neonates after reversal of neuromuscular effects of pancuronium. *Significantly different from group I* (P < 0.05)

		20 Hz/5 s			50 Hz/5 s		
	Train-of-four (%)	Fade (%)	Post-tetanic potentiation (%)	Tetanus: twitch ratio	Fade (%)	Post-tetanic potentiation (%)	Tetanus: twitch ratio
Group I							
Mean ± SEM	83.0 ± 1.8	4 ± 2	4 ± 3.5	2.2 ± 0.2	19 ± 3	−1 ± 1	2.6 ± 0.2
Range	80–90	0–16	−5–25	1.8–3	10–30	−12–7	2–4
Group II							
Mean ± SEM	94.6 ± 1.3*	4 ± 1	5 ± 3	3.0 ± 0.3	13 ± 3	5 ± 3	3.8 ± 0.4*
Range	89–100	0–11	−10–25	1.9–4	0–33	−12–30	2.2–5
Group III							
Mean ± SEM	91.4 ± 2.8*	6 ± 2	4 ± 2	3.1 ± 0.4	16 ± 3	2 ± 1	3.7 ± 0.4*
Range	80–100	0–18	0–20	2–5.5	0–25	0–13	2.2–6.2
Mean ± SEM of three groups	90.7 ± 1.4	4.7 ± 1.7	4.4 ± 1.7	2.8 ± 0.2	14.1 ± 0.7	2.3 ± 1.6	3.5 ± 0.23

tetanus : twitch ratios were significantly greater in infants older than 32 weeks of developmental age as compared with those less than 32 weeks-of-age. This deficiency may be caused by factors in the muscle itself, or at the neuromuscular junction. Dubowitz (1965, 1966) found, with histochemical techniques, type I fibres (slow-twitch, high-oxidative) in the peripheral muscles of postmortem specimens of fetuses and newborn infants 20–26 weeks of gestation that were larger in diameter and comprised only 3–10% of the total muscle fibres. From 30 weeks of gestation onwards, he noted a distinct subdivision into Type I and Type II (fast-twitch, low-oxidative), giving a checkerboard pattern with an approximately equal distribution of both types of fibres as in the muscle of older children and adults (Dubowitz 1965, 1966; Curless, 1977). Whether this observation has any correlation with our observation in the change of train-of-four and tetanus : twitch ratios is a matter for speculation. They do point in the same direction. Other factors observed in animals, such as a decrease in the number of tension-generating sites (Close, 1964) or a decrease in the safety factor (Kelly and Roberts, 1977) may be involved.

When we examined the train-of-four and tetanus : twitch ratio data and compared them with those from our previous study on maturation of neuromuscular junction (Goudsouzian, 1980), we noticed two apparent changes in neuromuscular indices: one at the age of 32 weeks of developmental age and another at the first month of extrauterine life (44 weeks developmental age) (fig. 4). The cause of these marked changes in neuromuscular indices at these particular dates is a matter for speculation. It remains to be determined if changes in muscle fibres or changes at the myoneural junction predominate.

We observed that the rate of fade either at 20 Hz or 50 Hz for 5 s was similar in the three groups of infants. We had made a similar observation between infants less than 1 and greater than 2 months of post-natal age (Goudsouzian, 1980). These data indicate that premature infants can sustain tetanus for a short time. If the duration of stimulation is prolonged to 15–20 s then infants (Churchill-Davidson and Wise, 1963), especially premature ones (Koenigsberger, Patten and Lovelace, 1973), show marked fade, indicating that premature infants can develop satisfactory tension for a short period (5 s), but that prolonged tetanus is poorly sustained. This is observed clinically in neonates when they initiate a muscle movement but are unable to maintain it. Also, with prolonged muscle contractions associated with coughing or breathing against high loads, premature infants fail more easily, and the only mechanism for compensation is rapid shallow breathing (short tetanic contraction) rather than deep breathing (long tetanic contraction).

In the present study, we demonstrated that the

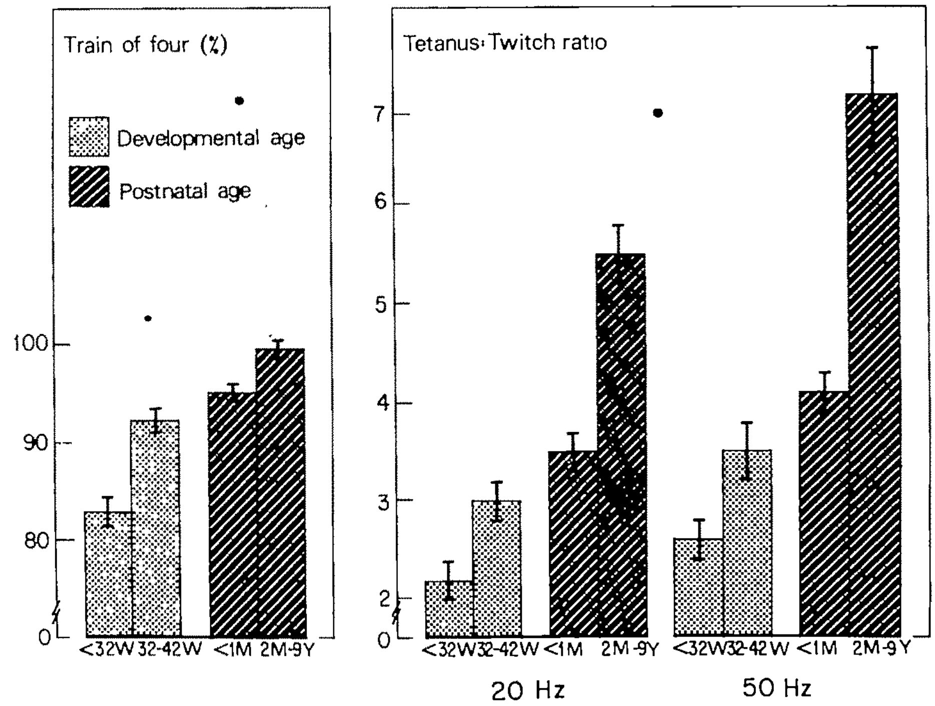

FIG. 4. The train-of-four values and tetanus : twitch ratios in the critically ill infants of the present study and the infants and children anaesthetized with halothane (Goudsouzian, 1980). W = (age in) weeks; M = months; Y = years.

evoked tension measurement technique used in the operating room to evaluate skeletal muscle contraction can be carried out with advantage in the neonatal intensive care unit. These techniques are also valuable in clarifying the aetiology of flaccidity in sick neonates who have received neuromuscular blocking agents. Infants with flaccidity from residual neuromuscular agents demonstrate low train-of-four, marked fade and post-tetanic facilitation with diminished tetanus : twitch ratios. Infants with severe central nervous system depression (for example severe intraventricular haemorrhage) have values within normal limits despite their flaccidity.

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REVEIL APRES BLOCAGE AU PANCURONIUM DANS UNE SALLE DE SOINS INTENSIFS POUR NOUVEAUX-NES

RESUME

Le blocage neuromusculaire à l'aide de pancuronium, de même que son antagonisme ont été évalués dans le cas de 33 bébés dangereusement malades. On a mesuré la contraction évoquée du muscle adducteur du pouce à partir d'une stimulation indirecte du nerf ulnaire. Le blocage neuromusculaire s'est remis spontanément des effets du pancuronium dans le cas de sept bébés, mais 23 d'entre eux ont eu besoin d'une ou de plusieurs doses d'atropine 0,02 ng kg^{-1} et de néostigmine 0,06 mg kg^{-1}. Chez les trois autres bébés le blocage ne s'est pas inversé. Les bébés immatures âgés de moins de 32 semaines n'ont présenté aucune différence significative dans leurs besoins en pancuronium, par rapport aux bébés plus mûrs. L'âgé et le poids à la naissance du bébé, la dose de pancuronium et la durée de son administration n'ont pas affecté les exigences nécessaires pour l'inversion. Rapports chaîne de quatre et tétanos: crispations ont été plus faibles ($P < 0{,}05$) chez les bébés âgés de moins de 32 semaines, ce qui reflète l'immaturité de la transmission musculaire.

ERHOLUNG VON DER PANCURONIUM-BLOCKADE IN DER INTENSIVBEHANDLUNGSEINHEIT FÜR NEUGEBORENE

ZUSAMMENFASSUNG

Die durch durch Pancuronium hervorgerufene neuromuskuläre Blockade und ihre Bekämpfung wurden bei 33 kritisch erkrankten Säuglingen ausgewertet. Die durch indirekte Stimulation des Ellennervs induzierte Kontraktion des Adduktor pollicis wurde gemessen. Die neuromuskuläre Blockade erholte sich spontan vom Pancuronium bei sieben Säuglingen; bei weiteren 23 war eine oder mehrere Dosen von Atropin 0,02 ng kg^{-1} und Neostigmin 0,06 mg kg^{-1} erforderlich. Bei 3 Säuglingen war die Blockade nicht mehr umzukehren. Im Vergleich zu voll entwickelten Säuglingen zeigten Säuglinge unter 32 Wochen keine bedeutende Unterschiede in Bezug auf ihren Bedarf an Pancuronium. Alter und Gewicht des Säuglings bei der Geburt, PancuroniumDosis und Verabreichungsperiode hatten keinen Einfluss auf die Voraussetzungen für den Umkehr. Viererfolge- und Tetanus: Zuckungsverhältnisse waren geringer ($P < 0{,}05$) bei Säuglingen unter 32 Wochen, was die unvollkommene Entwicklung der neuromuskuläre Übertragung wiederspiegelt.

RECUPERACION DEL BLOQUEO DE PANCURONIO EN LA SALA NEONATAL DE CUIDADOS INTENSIVOS

SUMARIO

Se evaluó, en 33 niños criticamente enfermos, el bloqueo neuromuscular con pancuronio y su antergia. Se midió la contracción provocada del pollicis abductor mediante la estimulación del nervio cubital. El bloqueo neuromuscular se recuperó espontáneamente del pancuronió en seis de los infantes; 23 necesitaron una o más dosis de 0,02 ng kg^{-1} de atropina y de 0,06 mg kg^{-1} de neostigmina. El bloqueo no pudo invertirse en tres de los pacientes. Los niños inmaduros de edades inferiores a las 32 semanas no mostraron ninguna diferencia significativa en sus necesidades de pancuronio, en comparación con los niños maduros. La edad y el peso al nacer, la dosis de pancuronio y la duración de la administración no afectaron las necesidades de la inversión. Relaciones series-en-cuatro y tétano: crispamiento eran inferiores ($P < 0{,}05$) en niños de edad inferior a 32 semanas de tiempo de desarrollo, reflejando asi immadurez de la transmisión neuromuscular.

Br. J. Anaesth. (1981), 53, 1311

PHARMACOKINETICS OF EDROPHONIUM IN ANEPHRIC AND RENAL TRANSPLANT PATIENTS

R. B. MORRIS, R. CRONNELLY, R. D. MILLER, D. R. STANSKI AND M. R. FAHEY

SUMMARY

The pharmacokinetics of edrophonium were determined in patients anaesthetized with nitrous oxide and halothane undergoing kidney transplant nephrectomy ($n = 6$) or transplantation of a live related donor kidney ($n = 6$). Serum concentrations of edrophonium were assayed by high pressure liquid chromatography and pharmacokinetic variables computed using non-compartmental analysis. Patients undergoing transplant nephrectomy had a significant increase in elimination half-life and a significant decrease (67%) in serum clearance when compared with kidney transplant recipients or patients with normal renal function. Pharmacokinetic indices for edrophonium in patients receiving a kidney transplant did not differ from those in patients with normal renal function. We conclude that absence of renal function decreases excretion of edrophonium to an extent similar to that of other acetylcholinesterase inhibitors, neostigmine and pyridostigmine.

Impaired renal function decreases plasma clearance and increases the duration of action of tubocurarine and pancuronium (Pavulon) in anaesthetized patients (Miller et al., 1977; Somogyi, Shanks and Triggs, 1977). This probably does not represent a clinical problem since renal failure also decreases the plasma clearance of the commonly used antagonists, neostigmine and pyridostigmine (Cronnelly et al., 1979, 1980). Recently, edrophonium 0.5–1.0 mg kg^{-1}, has been shown to produce sustained antagonism of non-depolarizing neuromuscular blockade (Bevan, 1979; Kopman, 1979; Morris et al., 1981). This study was designed to determine the influence of renal failure on the pharmacokinetics of edrophonium in anaesthetized patients.

METHODS

Informed consent, approved by our Committee on Human Research, was obtained from 12 adult patients. Six of these patients were about to undergo transplant nephrectomy (anephric group), and the six remaining patients were about to receive a living related kidney transplant (LRKT). Approximately 1 h after the oral administration of diazepam (Valium) 10 mg, anaesthesia was induced with thiopentone (Pentothal) 2–4 mg kg^{-1}, and maintained with halothane 0.4–0.7% (end-tidal) and 60% nitrous oxide in oxygen, measured by mass spectrometry. Tubocurarine was administered as an i.v. bolus with repeated doses sufficient to maintain approximately a 90% depression of twitch tension. At the end of surgery, the neuromuscular blockade was antagonized with edrophonium 1.0 mg kg^{-1} combined with atropine 1.0 mg administered as a 2-min i.v. infusion. Venous blood samples were obtained 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, 120, 180, 210 and 240 min after starting the infusion. Serum was stored at −30°C until extracted and assayed by high pressure liquid chromatography (De Ruyter, Cronnelly and Castagnoli, 1980). Data were treated using a non-compartmental pharmacokinetic analysis (Benet and Galeazzi, 1979) and differences determined by a Tukey's Test (Snedecor, 1962). Data previously obtained (Morris et al., 1981) from four patients with normal renal function who received edrophonium 1 mg kg^{-1} were analysed by non-compartmental pharmacokinetic analysis and included for comparison.

RESULTS

The slope of the elimination phase for the anephric group is less than that of patients with normal renal function, resulting in significantly greater serum

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concentrations of edrophonium in anephric patients after 4 h (fig. 1). The data from patients with normal renal function are taken from a previous study (Morris et al., 1981).

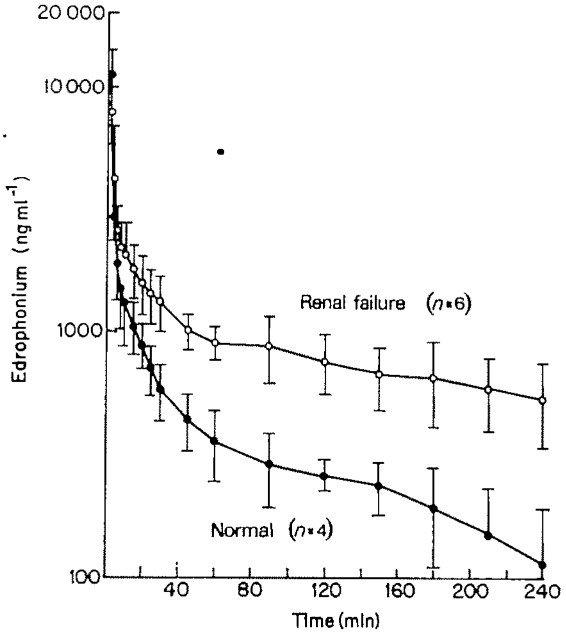

FIG. 1. Serum concentration following 2-min i.v. infusion of edrophonium 1.0 mg kg^{-1} in anaesthetized patients without renal function and with normal renal function. Points represent means ± SD.

Anephric patients had a significantly decreased plasma clearance and prolonged elimination half-life when compared with patients with normal renal function and with those patients who had received a kidney transplant (table I). Pharmacokinetics of edrophonium in patients who had received a kidney transplant were not different from those in patients with normal renal function (table I).

TABLE I. *Pharmacokinetics of edrophonium in anephric and renal transplant patients (means ± SD).* * *Significant difference ($P < 0.05$) from normal and transplant.* $T_{\frac{1}{2}}^{\beta}$ = *elimination half-life,* V^{ss} = *volume of distribution at steady state,* Cl = *clearance*

Patients	$T_{\frac{1}{2}}^{\beta}$ (min)	V^{ss} (litre kg^{-1})	Cl (ml kg min^{-1})
Normal	114.0 ± 47	0.87 ± 0.22	8.2 ± 2.7
Anephric	206.0 ± 62*	0.68 ± 0.13	2.7 ± 1.4*
Transplant	86.5 ± 23.9	0.92 ± 0.16	9.9 ± 2.1

DISCUSSION

When edrophonium is given in the absence of renal function, plasma clearance is decreased and elimination half-life prolonged to an extent similar to that of neostigmine and pyridostigmine (Cronnelly et al., 1979, 1980). Plasma clearance of edrophonium is 8.2 ± 2.7 ml kg^{-1} min^{-1} in normal patients and 2.7 ± 1.4 ml kg^{-1}min^{-1} in patients without renal function. Thus, approximately 67% of plasma clearance of edrophonium appears to be dependent on renal excretion, the remainder being dependent on non-renal mechanisms. If renal excretion occurred solely by glomerular filtration, renal clearance of 1–2 ml kg^{-1} min^{-1} would be expected (Melman and Morelli, 1978; Duchin and Sechrici, 1978). Larger values, such as 5.5 ml kg^{-1} min^{-1} reported here, suggest a tubular secretory process.

Since edrophonium is not hydrolysed by cholinesterase, this cannot contribute to non-renal clearance. Hepatic metabolism and biliary excretion have been demonstrated in animals (Back and Calvey, 1972; Calvey and Back, 1973) and represent probable pathways for non-renal clearance of edrophonium in man. In the patients receiving a living related kidney transplant, diuresis was induced before administration of edrophonium. Under these circumstances, the pharmacokinetics of edrophonium did not differ from those in patients with normal renal function. Similar findings have been reported for tubocurarine (Miller et al., 1977), neostigmine (Cronnelly et al., 1979) and pyridostigmine (Cronnelly et al., 1980).

Problems of prolonged neuromuscular blockade have occurred in patients with renal failure undergoing anaesthesia and surgery. Renal failure has been thought to prolong tubocurarine activity more than the antagonist activity of neostigmine and pyridostigmine (Miller and Cullen, 1976). If the plasma concentration is directly related to effect, antagonism by edrophonium should last longer than tubocurarine neuromuscular blockade in patients with renal failure. Consistent with this hypothesis are our observations of sustained antagonism of tubocurarine neuromuscular blockade even in the presence of renal failure.

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LA PHARMACOCINETIQUE DE L'EDROPHONIUM CHEZ LES PATIENTS SUBISSANT UNE NEPHRECTOMIE ET UNE GREFFE DU REIN

RESUME

On a déterminé la pharmacocinétique de l'édrophonium sur des patients anesthésiés au protoxyde d'azote et à l'halothane subissant une néphrectomie avec greffe du rein ($n = 6$) ou une greffe de rein provenant d'un donneur vivant apparenté ($n = 6$). Les concentrations d'édrophonium dans le sérum ont été analysées par la chromatographie en phase liquide à haute pression et les variables pharmacocinétiques ont été calculées à l'aide d'une analyse non compartimentée. Les patients subissant une néphrectomie avec greffe ont eu une augmentation significative de la demi-vie d'élimination et une diminution significative (67%) de l'épuration du sérum par rapport aux receveurs de greffes de rein ou aux patients dont les reins fonctionnaient normalement. Les indices pharmacocinétiques de l'édrophonium des patients subissant une greffe de rein n'ont pas différe de ceux des patients dont les reins fonctionnaient normalement. Nous en avons conclu que l'absence de fonction rénale diminue l'excrétion de l'édrophonium à un point similaire à celui des autres inhibiteurs acétylcholinestérases, de la néostigmine et de la pyridostigmine.

DIE PHARMAKOKINETIK VON EDROPHONIUM BEI NIERENLOSEN UND NIERENTRANSPLANTATIONSPATIENTEN

ZUSAMMENFASSUNG

Es wurde die Pharmakokinetik von Edrophonium bei Patienten bestimmt, die mit Stickoxydul und Halothan anästhesiert wurden und sich einer Nierentransplantationsnephrektomie ($n = 6$) bzw der Transplantation einer von einem verwandten Spender gestifteten Niere ($n = 6$) unterzogen. Serumkonzentrationen von Edrophonium wurden mittels Hochdruck-Flüssigkeitschromatographie ausgewertet und pharmakokinetische Variablen wurden mittels Analyse ohne Abteile ausgerechnet. Patienten, die sich einer Transplantationsnephrektomie unterzogen, zeigten eine bedeutende Steigerung der Eliminationshalbzeit und einen bedeutenden Abfall (67%) der Serumclearance im Vergleich zu Nierentransplantationspatienten oder Patienten mit normaler Nierenfunktion. Pharmakokinetische Indizien für Edrophonium bei Patienten, die eine Nierentransplantation bekamen, unterschieden sich nicht von denen bei Patienten mit normaler Nierenfunktion. Wir kamen zum Schluss, dass das Ausbleiben der Nierenfunktion die Absonderung von Edrophonium in ähnlichem Masse herabsetzt wie bei anderen Acetylcholinesterase-Inhibitoren, wie Neostigmin und Pyridostigmin.

FARMACOCINETICAS DEL EDROFONIO EN PACIENTES NEFRITICOS Y DE TRANSPLANTE DE RIÑON

SUMARIO

Se determinaron las farmacocinéticas del edrofonio en pacientes anestesiados con óxido nitroso y con halotano, sometidos a nefrectomía de transplante de riñón ($n = 6$) o a transplante de riñón vivo consanguíneo ($n = 6$). Las concentraciones de edrofonio en el suero se evaluaron mediante cromatografía de líquido a alta presión y las las variables farmacocinéticas se calcularon usando análisis sin compartimientos. Los pacientes sometidos a nefrectomía de transplante presentaron un incremento significativo en la vida media de la eliminación y una significativa disminución (67%) en la clarificación del suero, cuando se efectuó la comparacion con los receptores del transplante de riñón o con pacientes con funciones renales normales. Los índices farmacocinéticos relativos al edrofonio, en pacientes sometidos a transplante de

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COMPARISON OF ATROPINE AND GLYCOPYRROLATE IN A MIXTURE WITH PYRIDOSTIGMINE FOR THE ANTAGONISM OF NEUROMUSCULAR BLOCK

R. K. MIRAKHUR, L. P. BRIGGS, R. S. J. CLARKE, J. W. DUNDEE AND H. M. L. JOHNSTON

SUMMARY

Neuromuscular block was antagonized using pyridostigmine 250 μg kg^{-1} in two groups of 50 patients; one group received atropine 20 μg kg^{-1} and the other glycopyrrolate 10 μg kg^{-1} with the anticholinesterase drug. Atropine was associated with a greater initial tachycardia than was glycopyrrolate. The subsequent bradycardia was also greater in this group, although the decreases in heart rate were smaller than those generally observed following mixtures of atropine and neostigmine. Arrhythmias were transient and required no treatment in either group. Better control of secretions was achieved with glycopyrrolate.

Although neostigmine is the drug used most commonly to reverse residual neuromuscular block, pyridostigmine may have certain advantages such as a longer duration of action, a greater therapeutic ratio, and less pronounced muscarinic effects (Katz, 1967; Miller, 1976; Gyermek, 1977).

The advantages of glycopyrrolate over atropine as the antimuscarinic agent (Mirakhur, 1979) include greater stability of heart rate, better protection against secretions and absence of central effects (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977, Ostheimer, 1977; Baraka et al., 1980; Cozanitis et al., 1980).

In the present study, glycopyrrolate or atropine was administered with pyridostigmine during the reversal of neuromuscular block and their effects compared, emphasis being placed on the effects of the two drugs on heart rate and rhythm, and on oropharyngeal secretions.

PATIENTS AND METHODS

The study was carried out in 100 adult patients, free from any cardiovascular, respiratory, metabolic or endocrine disorder. All the patients gave informed consent and the study was approved by the Regional Ethics Committee. The patients were undergoing anaesthesia requiring the use of myoneural blocking drugs. Following premedication with diazepam by mouth, anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen and halothane or a combination of fentanyl and droperidol administered i.v. The two techniques of anaesthesia were administered in random fashion. Pancuronium was used to provide neuromuscular blockade. Fluids and blood were administered i.v. as appropriate. The adequacy of ventilation in all the patients was assessed by analyses of arterial blood-gas tensions and adjustments were made, if necessary, to maintain Pa_{CO_2} between 4.65 and 5.98 kPa. Before the administration of the reversal mixture, the oropharynx was sucked free of secretions. Lead II of the electrocardiogram (e.c.g.) was monitored throughout the operation. Recording was started 1 min before the administration of the antagonist mixture which consisted of pyridostigmine 250 μg kg^{-1} with glycopyrrolate 10 μg kg^{-1} or atropine 20 μg kg^{-1}. The anticholinergic drugs were administered double-blind from specially prepared, coded ampoules. The recording was continued until 10 min following the administration of the antagonizing mixture. Systolic arterial pressure was recorded at 1-min intervals during this time and then heart rate and arterial pressure were recorded at intervals, for a further 110 min, in

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the recovery ward (table II). A further increment of 1 ml of the anticholinergic drug (atropine 0.4 mg or glycopyrrolate 0.2 mg) was administered if the heart rate decreased to 50 beat min^{-1} or less in any patient.

As soon as the patient started to reject the endotracheal tube, the oropharynx was suctioned, secretions arbitrarily classified as "minimal", "moderate" or "excessive" and the trachea extubated.

The e.c.g.'s were analysed in detail for changes in rate and rhythm. Student's *t* tests were used for the statistical analyses of the changes in heart rate and a Chi-squared test for non-parametric data.

RESULTS

The 50 patients in each group were well matched with regard to their physical characteristics (table I).

Heart rates before the administration of the antagonist mixture were similar in both groups. There was no difference in the pattern of the changes in heart rate between the patients given fentanyl–droperidol or halothane for the maintenance of anaesthesia. Heart rates over the 120 min are shown in table II and the percentage change from values before antagonism in figure 1. The administration of the atropine-containing mixture increased the heart rate from 85 to a maximum of 98 beat min^{-1} (16%) at 1 min. The mean heart rate decreased subsequently and was less than control from 4 min, the maximal decrease being about 9% at 10 min. The increases at 1 and 2 min, and the decreases in rate from 4 to 90 min were significant.

The initial increase in heart rate in the group receiving glycopyrrolate was significant over the first 6 min, reaching a maximum of about 9% at 2 min. The rate remained not significantly greater than the control value for up to 20 min. Subsequently, this decreased marginally below the baseline heart rate. This decrease was significant at 50 min, although the heart rate had decreased only 4 beat min^{-1} at this time. Figure 1 demonstrates the difference in the pattern of the changes in heart rate between the two anticholinergic drugs. The atropine-containing mixture was associated with a significantly greater increase in heart rate at 1 min in comparison with the glycopyrrolate-containing mixture, but this was followed quickly by a greater decrease which was significant in comparison with the glycopyrrolate group between 4 and 10 min.

TABLE I. *Physical characteristics of the patients*

Group	Number	Mean age (yr ±SEM)	Mean weight (kg ±SEM)	Sex	
				M	F
Atropine	50	48±1.9	65±1.5	22	28
Glycopyrrolate	50	47±2.2	65±1.8	23	27

TABLE II. *Heart rates following the administration of atropine or glycopyrrolate combined with pyridostigmine (mean ± SEM) Significantly different from value before antagonism:* *P < 0.05; †P < 0.005; ***P < 0.001

Time (min)	Group	
	Glycopyrrolate	Atropine
Before antagonism	83±1.8	85±2.3
1	85±1.9	98±2.4***
2	90±2.1***	92±2.2***
3	90±2.2***	87±2.4
4	89±2.3†	81±2.5
5	88±2.2*	79±2.4*
6	88±2.2*	79±2.4†
7	86±2.2	79±2.3†
8	86±2.3	77±2.2***
9	87±2.3	77±2.1***
10	86±2.3	76±2.1***
20	81±1.9	78±2.2*
30	81±1.9	79±2.0*
40	80±1.8	80±2.0*
50	79±1.5*	79±1.8*
60	80±1.5	79±2.1*
75	81±1.7	79±1.9*
90	80±1.7	80±2.0*
105	81±1.8	81±1.9
120	81±1.8	81±1.9

The heart rate in three patients in the atropine group decreased to 50 beat min^{-1} or less. Two of these received one additional dose of atropine; one required two additional doses. This was not required in any of the patients receiving glycopyrrolate.

The frequency of arrhythmia (table III) was slightly greater in the group receiving atropine. One of the patients in this group showed persistent ventricular ectopic beats in a trigeminal fashion. Overall, the arrhythmias were not serious and did not warrant treatment.

Changes in arterial pressure were clinically insignificant in both groups.

Investigation of the amount of oropharyngeal secretions (table IV) showed that the group receiving glycopyrrolate had a higher proportion of patients with "minimal" secretions ($P < 0.01$).

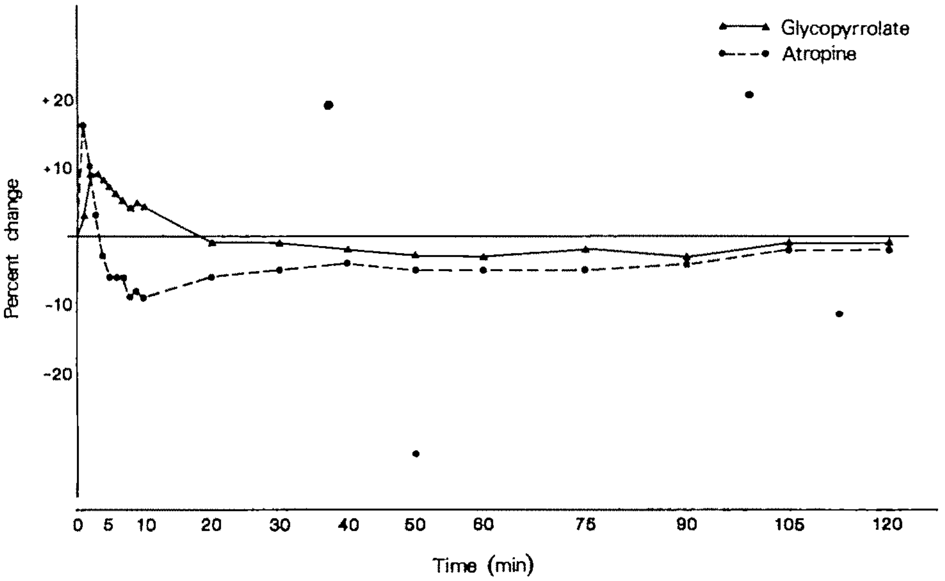

FIG. 1. Percentage changes in heart rate following the administration of reversal mixtures.

TABLE III. *Number of patients showing arrhythmia. *Present before antagonism in one patient; **Present before antagonism in two patients*

Group	Total number of patients	Increased PR interval	Nodal/ junctional rhythm	Wandering pacemaker	Atrial ectopic beats	Atrial tachycardia + increased QT interval	Ventricular ectopic beats
Atropine–pyridostigmine	13	0	3	2	1	1	6* (one in trigeminal fashion)
Glycopyrrolate–pyridostigmine	9	1	3	1	0	0	4**

TABLE IV. *Number of patients with various grades of oropharyngeal secretions. * Significantly different from atropine group* (P<*0.01*)

Group	Grade of secretion		
	Minimal	Moderate	Excessive
Atropine	13	33	4
Glycopyrrolate	28*	20*	2*

DISCUSSION

The present study demonstrated certain advantages in the use of glycopyrrolate, when compared with atropine, as the anticholinergic component of the antagonist mixture when pyridostigmine was used to antagonize residual neuromuscular block. There was less tachycardia immediately following administration of the drug and better protection against subsequent bradycardia. In addition, no patient receiving glycopyrrolate had a heart rate of 50 beat min^{-1} or less whereas a further administration of atropine was required in three patients in the atropine group. Similar results were reported when glycopyrrolate was used in a mixture with neostigmine (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977; Ostheimer, 1977; Cozanitis et al., 1980).

The present combination of pyridostigmine and atropine appears to be superior to the combination of neostigmine and atropine studied previously (Mirakhur et al., 1981) because bradycardia was less pronounced. Similar results were obtained by Eriksen, Hansen and Hasselstrom (1978). Only 6% of those patients in the present study receiving atropine and pyridostigmine required additional doses of atropine in comparison with 30% in our previous study in which atropine in a similar dose was administered with neostigmine (Mirakhur et al., 1981). In the study of Eriksen, Hansen and Hasselstrom (1978) greater initial increases in heart rate were observed with the use of atropine in a pyridostigmine-containing mixture, but the subsequent decreases in heart rate were also greater compared with glycopyrrolate.

The use of a combination of pyridostigmine and glycopyrrolate does not appear to have any advantages over a combination of glycopyrrolate with neostigmine when the data from the present study are compared with previous reports (Mirakhur, Dundee and Clarke, 1977; Cozanitis et al., 1980; Mirakhur et al., 1981). Muravchick, Owens and Felts (1979) found a mixture of glycopyrrolate and neostigmine to be superior to a mixture of glycopyrrolate and pyridostigmine in elderly patients. In contrast to our previous studies involving glycopyrrolate and neostigmine (Mirakhur, Dundee and Clarke, 1977; Mirakhur et al., 1981), a significant initial tachycardia was observed with the glycopyrrolate–pyridostigmine mixture, but this was significantly less than that produced by the atropine-containing mixture. This could be expected for two reasons. First, since pyridostigmine is known to possess less marked muscarinic effects than neostigmine (Katz, 1967; Miller, 1979), the effects of concomitantly administered anticholinergic drugs are consequently more pronounced. Second, the initial increase in heart rate induced by glycopyrrolate may be more apparent since the effects of this drug become evident before those of pyridostigmine. Mirakhur, Jones and Dundee (1981), have shown that glycopyrrolate exerts its peak effect at around 3–4 min, whereas Miller and colleagues (1974) noted that pyridostigmine acted in 5–6 min. Although the times to the peak action of glycopyrrolate and neostigmine may be alike (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977; Mirakhur et al., 1981), glycopyrrolate can be used safely with pyridostigmine. However, a combination of glycopyrrolate and pyridostigmine would be more appropriate on account of the long duration of action of both drugs.

A smaller number of patients in the glycopyrrolate group showed cardiac arrhythmias, although the differences were not significant. The use of glycopyrrolate has been associated with a lower frequency of arrhythmias when used with neostigmine (Klingenmaier et al., 1972; Ostheimer, 1977). However, experience with glycopyrrolate–neostigmine mixtures has shown the frequency to be similar to that of an atropine–neostigmine mixture, serious arrhythmias being absent (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977; Eriksen, Hansen and Hasselstrom, 1978; Mirakhur et al., 1981). However, when the frequency of arrhythmia in the present series is compared with data on neostigmine (Mirakhur et al., 1981) the frequency is less with pyridostigmine, irrespective of whether the anticholinergic is atropine or glycopyrrolate. A similar observation was made by Eriksen, Hansen and Hasselstrom (1978). Owens, Waldbaum and Stephen (1978) confirmed these results in elderly patients, although the latter group (Muravchick, Owens and Felts, 1979) subsequently found no differences when the drugs were administered on a weight-related basis.

Oropharyngeal secretions were controlled better, both qualitatively and quantitatively, with glycopyrrolate. This is a recognized feature of the drug and has been demonstrated consistently in combination with neostigmine (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977; Ostheimer, 1977) and pyridostigmine (Gyermek, 1977; Eriksen, Hansen and Hasselstrom, 1978). Glycopyrrolate has been reported to have a more selective antisialagogue effect (Mirakhur, Dundee and Jones, 1978; Mirakhur, 1979; Mirakhur and Dundee, 1980).

Although the potency ratio of pyridostigmine has been variously reported to be one-half (Gotta and Sullivan, 1970), one-eighth (Randall et al., 1955) or one-twentieth (Smith, Mead and Unna, 1957) that of neostigmine, more recent and accurate assessments have shown it to be around one-fourth to one-fifth (Fogdall and Miller, 1973; Miller et al., 1974; Miller, 1979). Our dosage of pyridostigmine 250 $\mu g\,kg^{-1}$, which is five times the usual dose of neostigmine 50 $\mu g\,kg^{-1}$, was appropriate clinically. All the patients could lift the head against gravity before leaving the operating room. Although at this time all the receptors may not be completely free of neuromuscular blocking agents, this test is nonetheless considered to be a sensitive index of recovery from neuromuscular block (Miller, 1976).

Although it is thought that pyridostigmine takes longer to exert its effect compared with neostigmine (Miller, 1976), care in the administration of the neuromuscular blocking drug with respect to dosage and time of administration helped us to achieve antagonism in a reasonable time. Extubation of the trachea was carried out at an average of 7 min following administration of the mixture and the ability to raise the head was attained within 10 min. This is similar to our experience with neostigmine.

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COMPARAISON DE L'ATROPINE ET DU GLYCOPYRROLATE PREPARES EN SOLUTION AVEC DE LA PYRIDOSTIGMINE COMME ANTAGONISTE DU BLOCAGE NEUROMUSCULAIRE

RESUME

On a provoqué l'antagonisme du blocage neuromusculaire en utilisant 250 $\mu g\ kg^{-1}$ de pyridostigmine sur deux groupes de 50 patients; un groupe a reçu 20 $\mu g\ kg^{-1}$ d'atropine et l'autre groupe a reçu 10 $\mu g\ kg^{-1}$ de glycopyrrolate associé au médicament anticholinestérase. L'atropine a été associée à une tachycardie initiale plus prononcée que ne l'a été le glycopyrrolate. La bradycardie qui a suivi a aussi été plus prononcée dans ce groupe, bien que les diminutions de la fréquence cardiaque aient été plus faibles que celles que l'on constate normalement après l'administration de mélanges d'atropine et de néostigmine. Les arythmies ont été transitoires et n'ont exigé aucun traitement dans aucun des deux groupes. On a obtenu une meilleure régulation des sécrétions avec le glycopyrrolate.

VERGLEICH VON ATROPIN UND GLYCOPYRROLAT IN EINER MISCHUNG MIT PYRIDOSTIGMIN BEI DER BEKÄMPFUNG VON NEUROMUSKULÄRER BLOCKADE

ZUSAMMENFASSUNG

Die neuromuskuläre Blockade wurde bei zwei Gruppen von 50 Patienen mittels Pyridostigmin 250 µg kg^{-1} bekämpft; die eine Gruppe bekam Atropin 20 µg kg^{-1} und die andere bekam Glycopyrrolat 10 µg kg^{-1} zusammen mit der Anticholinesterasedroge. Atropin zeichnete sich durch eine stärkere anfängliche Tachykardie als Glycopyrrolat aus. Die anschliessende Bradykardie war ebenfalls grösser als bei der ersten Gruppe, obwohl die Verringerungen des Herzschlags geringer waren als die, die im allgemeinen bei Mischungen von Atropin und Neostigmin beobachtet werden. Arrhythmien waren von kurzer Dauer und erforderte bei keiner der beiden Gruppen eine Behandlung. Eine bessere Kontrolle der Sekretionen wurde mit Glycopyrrolat erreicht.

COMPARACION DE LA ATROPINA Y DEL GLICOPIRROLATO CON LA PIRIDOSTIGMINA EN UNA MEZCLA EN LO TOCANTE A LA ANTERGIA DEL BLOQUEO NEUROMUSCULAR

SUMARIO

Se contrarrestó el bloqueo neuromuscular en dos grupos de 50 pacientes, usando 250 µg kg^{-1} de piridostigmina; un grupo recibió 20 µg kg^{-1} de atropina y el otro grupo recibió 10 µg kg^{-1} de glicopirrolato, junto con la droga anticolinesterasa. La atropina vino asociada con una mayor taquicardia inicial de lo que lo fue el glicopirrolato. La bradicardia subsiguiente fue también superior en este grupo, aunque las disminuciones del ritmo cardiaco fueron menores que las que se observaron, por lo general, a raíz de las mezclas de atropina y de neostigmina. Las arritmias fueron momentáneas y no necesitaron tratamiento alguno en ninguno de los grupo. Usando el glicopirrolato se obtuvo un mejor control de las secreciones.

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LACK OF EFFECT OF KETAMINE ANALGESIA ON GASTRIC EMPTYING IN MAN

I. S. GRANT, W. S. NIMMO AND J. A. CLEMENTS

SUMMARY

The effect of ketamine analgesia on gastric emptying was assessed in five healthy volunteers. Gastric emptying, estimated indirectly by the absorption of orally administered paracetamol, was not significantly delayed following administration of i.m. ketamine when compared with placebo.

Ketamine is a potent analgesic which may have some advantages in the period after operation by avoiding the respiratory and cardiovascular depressant effects of the narcotic analgesic drugs (Sadove et al., 1971). One major side-effect of all narcotic analgesics is a delay in gastric emptying and gastrointestinal transit which may contribute to nausea and vomiting and prevent patients recommencing oral fluids, food and medication in the early period after operation (Nimmo, Wilson and Prescott, 1975; Nimmo et al., 1978). It is not known if ketamine in analgesic doses produces similar effects.

In the present study, we have investigated the effect of ketamine on gastric emptying in healthy volunteers, using the rate of paracetamol absorption as an index of gastric emptying rate. Paracetamol, a safe analgesic drug, is not absorbed to any extent from the stomach, but is readily absorbed from the upper small intestine. Thus, the rate of gastric emptying determines the rate of absorption of orally administered paracetamol. Simultaneous measurements of paracetamol absorption and gastric emptying have confirmed that measurement of the rate of absorption of orally administered paracetamol is a reliable estimate of gastric emptying (Nimmo et al., 1975, 1979; Clark et al., 1980). Rapid paracetamol absorption indicates rapid gastric emptying, whereas delayed paracetamol absorption reflects delayed gastric emptying.

SUBJECTS AND METHODS

Five healthy volunteers (aged 30–39 yr, weight 65–84 kg) were each studied on two occasions in random order at least 1 week apart, once after i.m. ketamine 0.5 mg kg^{-1} and once after i.m. injection of saline. Ketamine 0.5 mg kg^{-1} i.m. results in analgesic plasma concentrations (>150 ng ml^{-1}) from 15 to 45 min after injection without impairment of consciousness (Grant, Nimmo and Clements, 1981). The mean plasma ketamine concentration in six volunteers 20 min after this dose was 190 ± 24 ng ml^{-1} ($\pm$SEM).

After an overnight fast, and 20 min after the i.m. injection, the subjects received paracetamol 20 mg kg^{-1} dissolved in 200 ml of orange juice. Venous blood samples were taken from an indwelling cannula before paracetamol administration and at 15, 30, 45, 60, 75, 90 and 120 min afterwards. The plasma was separated and stored at -20 °C until measurement of plasma paracetamol concentrations by high performance liquid chromatography (Howie, Adriaenssens and Prescott, 1977).

Paracetamol absorption was assessed from the plasma concentrations at each sampling time, the peak concentrations and the times to reach peak concentration. Statistical analyses were carried out using Student's *t* test.

RESULTS

Paracetamol absorption (and hence gastric emptying) was normal following placebo in all five subjects, with a mean peak paracetamol concentration of 20.3 ± 2.3 μg ml^{-1} ($\pm$SEM). The mean time of the peak concentration was 36 ± 7.6 min after ingestion (table I).

After ketamine 0.5 mg kg^{-1} i.m., there was no significant delay in paracetamol absorption, a

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TABLE I. *Lack of effect of ketamine on paracetamol absorption in five subjects*

Group	Mean peak plasma paracetamol concn ($\mu g\,ml^{-1} \pm$ SEM)	Mean time of peak concentration (min ± SEM)
Placebo	20.3±2.3	36±7.6
Ketamine	23.8±5.3	63±16

mean peak paracetamol concentration of $23.8 \pm 5.3\,\mu g\,ml^{-1}$ occurring 63±16 min after ingestion. At no sampling time did the concentrations differ significantly from the placebo group (fig. 1).

In only one subject was there any delay in paracetamol absorption following ketamine, with a paracetamol concentration of $7.2\,\mu g\,ml^{-1}$ 120 min after ingestion. A peak concentration of $17.9\,\mu g\,ml^{-1}$ was achieved 45 min after placebo.

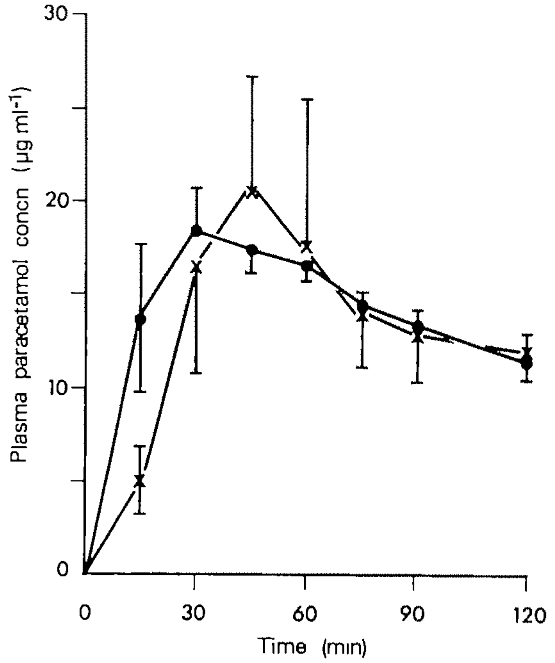

FIG. 1. Paracetamol absorption in five healthy volunteers following ketamine $0.5\,mg\,kg^{-1}$ i.m. (×) and placebo (●). Mean plasma paracetamol concentrations ± SEM ($\mu g\,ml^{-1}$).

DISCUSSION

Ketamine in analgesic concentrations probably does not influence gastric emptying. Paracetamol absorption was almost identical in all but one of the subjects in the ketamine and control studies. In a similar study, pentazocine 60 mg i.m. given to healthy volunteers 30 min before paracetamol $20\,mg\,kg^{-1}$ produced a marked delay in paracetamol absorption in all subjects. The mean peak paracetamol concentration was $10.8\,\mu g\,ml^{-1}$ at 160 min (control $23.8\,\mu g\,ml^{-1}$ at 23 min) (Nimmo et al., 1979). Similar delay has been noted following pethidine 150 mg i.m. and diamorphine 10 mg i.m. (Nimmo et al., 1975).

Only one individual in this study experienced any delay in paracetamol absorption. Anxiety and sympathetic overactivity may have contributed to delay in this case (Rees et al., 1980).

Ketamine has been used as a postoperative analgesic which avoids several of the side-effects of narcotic analgesics (Ito and Ichiyanagi, 1974; Slogoff et al., 1974). In this study we have demonstrated that, in an analgesic dose, it has no significant effect on gastric emptying. This finding is consistent with a recent study reporting that ketamine has no effect on gastrointestinal activity in greyhounds (Healy et al., 1981). It may represent another advantage of the drug.

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MANQUE D'EFFET DE L'ANALGESIE INDUITE A L'AIDE DE KETAMINE SUR LE VIDAGE GASTRIQUE CHEZ L'HOMME

RESUME

On a évalué sur cinq volontaires en bonne santé l'effet qu'a l'analgésie induite à l'aide de kétamine sur le vidage gastrique. Le vidage gastrique, estimé indirectement par l'absorption de paracétamol administré par voie buccale, n'a pas été retardé de façon significative après l'administration intramusculaire de kétamine, ceci par comparaison à un placébo.

WIRKUNGSLOSIGKEIT VON KETAMIN-ANALGESIE BEI DER MAGENENTLEERUNG BEIM MENSCHEN

ZUSAMMENFASSUNG

Die Wirkung von der Ketamin-Analgesie bei der Magenentleerung wurde bei fünf gesunden Freiwilligen ausgewertet. Die Magenentleerung, indirekt durch die Absorption von oral verabreichtem Paracetamol geschätzt, wurde nicht bedeutend nach intramuskulärer Verabreichung von Ketamin verzögert, verglichen mit einem Suggestionsmittel.

AUSENCIA DE EFECTO ALGUNO DE LA ANALGESIA MEDIANTE KETAMINA SOBRE EL VACIADO GASTRICO DEL HOMBRE

SUMARIO

Se evaluó el efecto analgésico de la ketamina en el vaciado gástrico de cinco pacientes sanos. El vaciado gástrico, que se estimó indirectamente por la absorción de paracetamol administrado oralmente, no se retrasó significativamente después de la administración de ketamina intramuscular, cuando se efectuó la comparación con el placebo.

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EQUALITY OF THE *IN VIVO* AND *IN VITRO* OXYGEN-BINDING CAPACITY OF HAEMOGLOBIN IN PATIENTS WITH SEVERE RESPIRATORY DISEASE

E. DOMÍNGUEZ DE VILLOTA, M. T. GARCÍA CARMONA, J. J. RUBIO AND S. RUIZ DE ANDRÉS

SUMMARY

The *in vivo* and *in vitro* oxygen-binding capacity of haemoglobin was determined on 10 occasions in nine patients who required mechanical ventilation. The *in vitro* sample was tonometered with 97% oxygen for 10 min and then with air, while the *in vivo* sample was obtained after 20 min of lung ventilation with pure oxygen. Subsequent laboratory procedures were identical for both samples. The mean oxygen-binding capacity of haemoglobin *in vitro* and *in vivo* samples were almost equal (1.365 ± 0.010 and 1.366 ± 0.007 ml per g Hb). When the measured inactive fractions of haemoglobin (carboxy- and methaemoglobin) were taken into account, these values increased to 1.392 ± 0.005 and 1.392 ± 0.007 ml per g Hb respectively.

The oxygen-binding capacity of haemoglobin is more frequently determined *in vitro* (Foëx et al., 1970; Theye, 1970; Bursaux, Dubos and Poyart, 1971; Gregory and Millar, 1973; Gregory, 1974; Dominguez de Villota et al., 1976, 1979; Dijkhuizen et al., 1977; Guillot et al., 1979) than *in vivo* (Gregory, Hulands and Millar, 1971, 1972; Gregory and Millar, 1973; Scherrer and Bachofen, 1972). Simultaneous *in vivo* and *in vitro* determinations have only been reported twice and from the same laboratory in healthy subjects (Gregory, Hulands and Millar, 1972; Gregory and Millar, 1973). In the present study, we investigated the oxygen-binding capacity of haemoglobin in seriously ill patients using both methods.

PATIENTS AND METHODS

Ten blood samples were obtained from nine patients, seven men and two women (mean age 66.5 ± 7.3 yr). Samples 4 and 8 were from the same patient, but were taken 3 weeks apart. In all patients the lungs were ventilated mechanically because of acute or chronic respiratory insufficiency.

Ten millilitre of arterial blood was withdrawn from an indwelling catheter and refrigerated immediately (*in vitro* sample), while the lungs were ventilated with variable concentrations of inspired oxygen; the mean Pa_{O_2} was 8.59 ± 1.49 kPa. The ventilator was then set to deliver FI_{O_2} 1.0 for 20 min before the withdrawal of another 10 ml of blood (*in vivo* sampling). This FI_{O_2} produced a mean Pa_{O_2} of 26.73 ± 7.78 kPa measured at 37 °C in a Comby-Analysator (Eschweiler & Co., Kiel).

Both samples were divided into two aliquots. The *in vitro* aliquots were tonometered (Eschweiler & Co, Type II, 40-ml capacity) at 37 °C with a saturated water vapour gas mixture of 97% oxygen and 3% carbon dioxide 10 min and subsequently with air for an equal period of time. The *in vivo* aliquots were processed immediately.

The oxygen content was determined in the four aliquots by the Van Slyke micromanometric technique (Van Slyke and Plazin, 1961). The dissolved oxygen ($Pa_{O_2} \times 0.0031$) was subtracted from the measured value to obtain the amount of oxygen combined with haemoglobin. This we refer to as "oxygen content". The concentration of haemoglobin (Hb) was measured by the cyanmethaemoglobin technique in a spectrophotometer (Beckman DU-2, Beckman Instruments Inc., Ill., U.S.A.) according to the International Standards (International Committee for Standardization in Haematology, 1978). Similarly, the fraction of methaemoglobin (MeHb) was measured in the same apparatus according to the technique of Hegesh and others (1970). A Co-Oximeter (IL 182, Instrumentations

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Laboratories Inc., Mass., U.S.A.) was used to measure the fraction of carboxyhaemoglobin (COHb). The co-oximeter was adjusted to read 99% of oxyhaemoglobin when blood from a non-smoker and tonometered with 97% oxygen was measured (Domínguez de Villota et al., 1976).

The oxygen-binding capacity of Hb was derived from the equation:

$$\text{Oxygen-binding capacity of Hb (ml g}^{-1}\text{)} = \frac{\text{maximal oxygen content (ml dl}^{-1}\text{)}}{\text{Hb concentration (g dl}^{-1}\text{)}}$$

The value of Hb obtained by the cyan-methaemoglobin method was corrected according to the concentrations of COHb and MeHb which were calculated from their measured fractions. The reduced value of Hb represented the amount of "functional Hb" and was used to calculate the corrected oxygen-binding capacity of Hb as follows:

$$\text{Corrected oxygen-binding capacity of Hb (ml g}^{-1}\text{)} = \frac{\text{maximal oxygen content (ml dl}^{-1}\text{)}}{\text{functional Hb (g dl}^{-1}\text{)}}$$

The results of the two determinations performed in each of the *in vivo* and *in vitro* samples were averaged and the mean used for statistical comparison (Student's *t* test for paired data).

RESULTS

The differences between duplicate measurements in this study were similar to those reported previously (Domínguez de Villota et al., 1976, 1979) (table I). The sum of the fractions of COHb and oxyhaemoglobin in the 80 individual measurements performed in the co-oximeter had a mean value of 99.8 ± 0.8%.

TABLE I. *Mean of differences between duplicate measurements with the techniques used*

	Number	Mean	SD	Range
Haemoglobin (g dl^{-1})	20	0.07	0.09	0.00–0.3
Carboxyhaemoglobin (%)	20	0.07	0.07	0.00–0.2
Oxygen content (ml dl^{-1})	20	0.18	0.12	0.00–0.45
Methaemoglobin (%)	10	0.007	0.009	0.00–0.02

The mean value of the oxygen-binding capacity of Hb, uncorrected for the inactive fractions of Hb, was 1.366 for the *in vivo* and 1.365 ml per g Hb for the *in vitro* samples. When the inactive fractions of Hb were taken into account, both values increased to 1.392 ml per g Hb. No significant differences were found in the paired comparison of the *in vivo* and *in vitro* determinations (table II).

TABLE II. *Mean values of the measurements performed. No significant differences* ($P > 0.05$) *were found by Student's test for paired data*

	In vivo	*In vitro*
Haemoglobin	10.79	10.66
(g dl^{-1})	(1.46)	(1.41)
Carboxyhaemoglobin	1.23	1.31
(%)	(0.52)	(0.60)
Oxygen content	14.75	14.55
(ml dl^{-1})	(2.04)	(1.95)
Methaemoglobin	—	0.62
(%)		(0.10)
"Functional" haemoglobin	10.59	10.45
(g dl^{-1})	(1.45)	(1.39)
Oxygen-binding capacity	1.366	1.365
(uncorrected)	(0.007)	(0.010)
(ml per g Hb)	1.354–1.376	1.352–1.379
Oxygen-binding capacity	1.392	1.392
(corrected)	(0.007)	(0.005)
(ml per g Hb)	1.384–1.405	1.384–1.399

DISCUSSION

There are few reported values of the oxygen-binding capacity of Hb calculated *in vivo*. In two non-smokers the mean values of nine measurements were 1.403 and 1.394 ml per g Hb (Gregory, Hulands and Millar, 1971). The same investigators reported, for their own blood, values close to 1.39 ml per g Hb in two, but significantly less in the other (Gregory, Hulands and Millar, 1972). Later they analysed blood from the first two subjects again and the values found were 1.316 and 1.331 in the same subject on separate days and 1.304 ml per g Hb for the second subject (Gregory and Millar, 1973). The values of COHb and MeHb in these studies were less than 1%. In 88 non-smokers, an oxygen-binding capacity of 1.39 ml per Hb was found; 0.15 g of Hb per dl of blood was bound to CO and 0.20 g of Hb per dl of blood was considered inactive (Scherrer and Bachofen, 1972).

In the present report, nine critically ill patients requiring mechanical ventilation of the lungs were studied. The maximum oxygen tensions attained were less than those reported in other *in vivo* work

(Gregory, Hulands and Millar, 1971, 1972; Scherrer and Bachofen, 1972) because of respiratory impairment. The Hb concentrations were also reduced compared with normal and with other studies (Scherrer, Kung and Moshi, 1971). However, our results for oxygen-binding capacity are similar to some of the *in vivo* values given above.

The *in vitro* measurements of the oxygen-binding capacity of Hb in non-smokers reported vary considerably with values of 1.30 (Theye, 1970), 1.31 (Bursaux, Dubos and Poyart, 1971; Gregory, 1974), 1.32 (Gregory and Millar, 1973), 1.33 (Gregory and Millar, 1973; Gregory, 1974), 1.34 (Foëx et al., 1970), 1.35 (Guillot et al., 1979), 1.36 (Domínguez de Villota et al., 1976, 1979) and 1.37 (Dijkhuizen et al., 1977). These values increased to 1.39 ml per g Hb when the fraction of inactive Hb was considered (Domínguez de Villota et al., 1976; Guillot et al., 1979). In smokers, values were less: 1.26 and 1.20 (Bursaux, Dubos and Poyart, 1971), 1.30 (Domínguez de Villota et al., 1976, 1979) and 1.33 (Guillot et al., 1979), but again the corrected figures increased to 1.39 (Domínguez de Villota et al., 1976, 1979) or exceeded it (Guillot et al., 1979).

This variability of values for oxygen-binding capacity exists not only between different investigators but even between reports from the same laboratory (Gregory, Hulands and Millar, 1971, 1972; Gregory and Millar, 1973; Dijkhuizen et al., 1977) and it has prompted discussion about the most physiological value (Theye, 1971; Prys-Roberts, Foëx and Hahn, 1971; Scherrer and Bachofen, 1972; Gregory, 1974; Dijkhuisen et al., 1977).

The possible influence of different methods of determining the *in vivo* and *in vitro* values in the variability of the oxygen-binding capacity of Hb has been mentioned (Scherrer and Bachofen, 1972). However, a comparison of the two methods of measurement in our study showed no significant difference. True variability of the oxygen-binding capacity of Hb has been suggested to explain the values obtained (Foëx et al., 1970; Prys-Roberts, Foëx and Hahn, 1971; Domínguez de Villota et al., 1976). The consistency of our results obtained from ambulatory patients *in vitro* (Domínguez de Villota et al., 1976), from healthy smokers *in vitro* (Domínguez de Villota et al., 1979) and from critically ill patients *in vivo* and *in vitro* support the concept of a constant value of the oxygen-binding capacity of Hb despite variability of individual measurements.

The accuracy of the Van Slyke technique in measuring the oxygen content is not debated (Theye, 1971; Gregory, 1973), but inaccurate measurement of Hb (Theye, 1971; Gregory, 1974) or the existence of a fraction of Hb not available to combine with oxygen (Scherrer and Bachofen, 1972; Dijkhuisen et al., 1977) but measurable by spectrophotometry (Dijkhuizen et al., 1977) have been suggested to explain values of oxygen-binding capacity less than 1.39 ml per g Hb. Approximately 1% of the total Hb was found unable to combine with oxygen even after tonometry for 150 min with pure oxygen (Dijkhuizen et al., 1977). The fact that our binding capacity of Hb, once corrected for the fractions of COHb and MeHb, reached the value of 1.39 ml per g Hb might be explained by calibration of the co-oximeter, with an offset of 1%. This 1% might have been an excessive allowance for patients who had been ill for some time and compensated for this small fraction of inactive Hb (Dijkhuizen et al., 1977), thus increasing our value of the oxygen-binding capacity of Hb to the theoretical maximum of 1.39 ml per g Hb.

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EGALITE DE LA CAPACITE *IN VIVO* ET *IN VITRO* QU'A L'HEMOGLOBINE DE LIER L'OXYGENE CHEZ LES PATIENTS SOUFFRANT D'UNE GRAVE MALADIE RESPIRATOIRE

RESUME

Il a été déterminé dans 10 cas la capacité *in vivo* et *in vitro* qu'a l'hémoglobine de lier l'oxygène, sur neuf patients qui avaient besoin de ventilation mécanique. L'échantillon *in vitro* a été soumis à une sphygmotonométrie à l'aide de 97% d'oxygène pendant 10 min puis à l'aide d'air, tandis que l'échantillon *in vivo* a été obtenu après une ventilation des poumons à l'oxygène pur pendant 20 min. Les processus suivis ultérieurement en laboratoire ont été les mêmes pour les deux échantillons. La capacité moyenne de lier l'oxygène qu'avait l'hémoglobine des échantillons *in vivo* et *in vitro* a été presque la même (1,365 ± 0,010 et 1,366 ± 0,007 ml par g Hb). Lorsqu'on a tenu compte des fractions inactives mesurées de l'hémoglobine (carboxy et méthémoglobine), ces valeurs sont passées à 1,392 ± 0,005 et 1,392 ± 0,007 ml par g Hb respectivement.

GLEICHHEIT DER SAUERSTOFFBINDENDEN FÄHIGKEIT VON HÄMOGLOBIN *IN VIVO* UND *IN VITRO* BEI PATIENTEN MIT SCHWEREN ATMUNGSKRANKHEITEN

ZUSAMMENFASSUNG

Die sauerstoffbindende Fähigkeit von Hämoglobin *in vivo* und *in vitro* wurde in 10 Fällen bei 9 Patienten festgestellt, die mechanische Ventilation benötigten. Das *in vitro* Muster wurde 10 Minuten lang mit 97%-igem Sauerstoff und anschliessend mit Luft equilibriert, während das *in vivo* Muster durch 20 Minuten lange Lungenventilation mit reinem Sauerstoff gewonnen wurde. Die anschliessenden Laborverfahren waren für beide Muster gleich. Die mittlere sauerstoffbindende Fähigkeit von Hämoglobin *in vivo* und *in vitro* war fast gleich (1,365 ± 0,010 und 1,366 ± 0,007 ml per g Hb). Als die gemessenen inaktiven Fraktionen von Hämoglobin (Kohlenmonoxydhämoglobin und Methämoglobin) in Betracht gezogen wurden, stiegen diese Werte auf 1,392 ± 0,005 bzw 1,392 ± 0,007 ml per g Hb.

IGUALDAD DE LA CAPACIDAD DE LA HEMOGLOBINA, *IN VIVO* E *IN VITRO*, PARA UNIRSE AL OXIGENO, EN PACIENTES CON GRAVES ENFERMEDADES RESPIRATORIAS

SUMARIO

Se determinó la capacidad de la hemoglobina, *in vivo* e *in vitro*, para unirse al oxígeno, en 10 ocasiones, efectuándose las pruebas en 9 pacientes que necesitaron ventilación mecánica. La muestra *in vitro* se sometió al esfigmomanómetro con un 97% de oxigeno por espacio de 10 min y, seguidamente, con aire, mientras que la muestra *in vivo* se obtuvo después de 20 min de ventilar los pulmones con oxígeno puro. Los subsiguientes procedimientos de laboratorio fueron idénticos para ambas muestras. La capacidad media de unión con el oxigeno, por parte de la hemoglobina *in vivo* e *in vitro*, fue casi igual para ambas muestras (1,365 ± 0,010 y 1,366 ± 0,007 ml por Hb. Cuando las fracciones de hemoglobina inactiva medidas (carboxihemoglobina y metahemoglobina) se tuvieron en cuenta, estos valores aumentaron hasta 1,392 ± 0,005 y 1,392 ± 0,007 ml por g Hb, respectivamente.

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EFFECT OF A NEW ANALGESIC, MR 1268, ON CIRCULATORY AND RESPIRATORY INDICES IN VOLUNTEERS

I. O. SAMUEL, R. S. J. CLARKE, J. W. DUNDEE AND J. J. WILSON

SUMMARY

MR 1268, a benzmorphan derivative with marked morphine-like properties and weaker antagonist properties was administered to six healthy male volunteers who each received MR 1268 2.5, 5, 10 and 20 mg i.v. in random order. There were no significant changes in the cardiovascular indices measured. However, significant and dose-related decreases in expired minute volume were observed. With 20 mg, consistent increases in Pa_{CO_2} coincided with maximum decrease in ventilation, indicating some degree of alveolar hypoventilation. Drowsiness was dose-related but of short duration and only significant with 20 mg. Pupillary size and reaction remained unaffected.

MR1268 [3-(2-methyl-3-furylmethyl)-1,2,3,4,5,6-hexahydro-6, 11-dimethyl-2, 6-methano-3-benzazocin-8-ol-methansulphonate] is a benzmorphan derivative (fig. 1) with marked morphine-like properties and weaker antagonist properties. It has been synthesized by Boehringer Ingelheim in an attempt to produce an acceptable, non-habit-forming analgesic with a satisfactory duration of action.

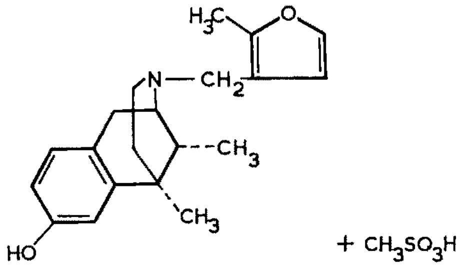

FIG. 1. Structural formula of MR 1268.

Experiments on mice (J. H. Shelley personal communication) have shown that, when given parenterally, the drug has 1–2 times the potency of pentazocine and between one-third and the same as that of morphine. Its duration of action is intermediate between the two compounds. The antagonist effect was demonstrated in mice by injecting morphine and MR 1268 simultaneously into two different sites and noting a less marked analgesic effect compared with animals receiving morphine alone. Like pentazocine, it does not produce a nalorphine-like intensifying effect on withdrawal symptoms. It would appear that MR 1268 has the pentazocine-like advantages over morphine in being a potent analgesic with little dependence-producing properties.

Preliminary studies of the analgesic action of MR 1268, carried out in West Germany in 1978, showed that 2.5–10 mg s.c. gave relief of pain following abdominal operations with minimal side-effects. Further studies with 15–30 mg i.m. suggested that MR 1268 was approximately equipotent with pentazocine. Subjective side-effects were trivial and there was no evidence of the psychotomimetic problems which decrease the acceptability of pentazocine (Beaver et al., 1966; Hamilton et al., 1967).

The present study was designed to assess the cardiovascular and respiratory side-effects of a wide range of doses of MR 1268 i.v. to volunteers, including "no measureable effect" at the lower (2.5 mg) and significant respiratory depression at the upper (20 mg) end. These volunteer studies enabled the effects of the drug to be evaluated in the absence of depressant anaesthetic agents and permitted assessment of subjective tolerance. The i.v. route ensured rapid and predictable uptake and accentuated the occurrence of side-effects.

SUBJECTS AND METHODS

Six volunteer anaesthetists were studied. Each was given a brochure summarizing the action of the

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drug and the potential hazards of the investigation. The study was approved by the local ethics committee.

The ages of the subjects ranged from 26 to 47 yr and their weights from 60 to 75 kg. Following overnight starvation they rested on a tilting couch for at least 30 min before the study commenced. An i.v. infusion was started and as MR 1268 was injected some distance from the site of venepuncture and out of the subject's view, they did not know the precise moment of administration. Each received MR 1268 2.5, 5, 10 and 20 mg. Apart from the initial dose of 2.5 mg, these were given in random order in a single-blind fashion, the subjects themselves being unaware of the dose they were receiving. The time interval between the studies in a particular volunteer was not less than seven days.

The plan of the study is shown diagramatically in figure 2, the following indices being recorded where shown:

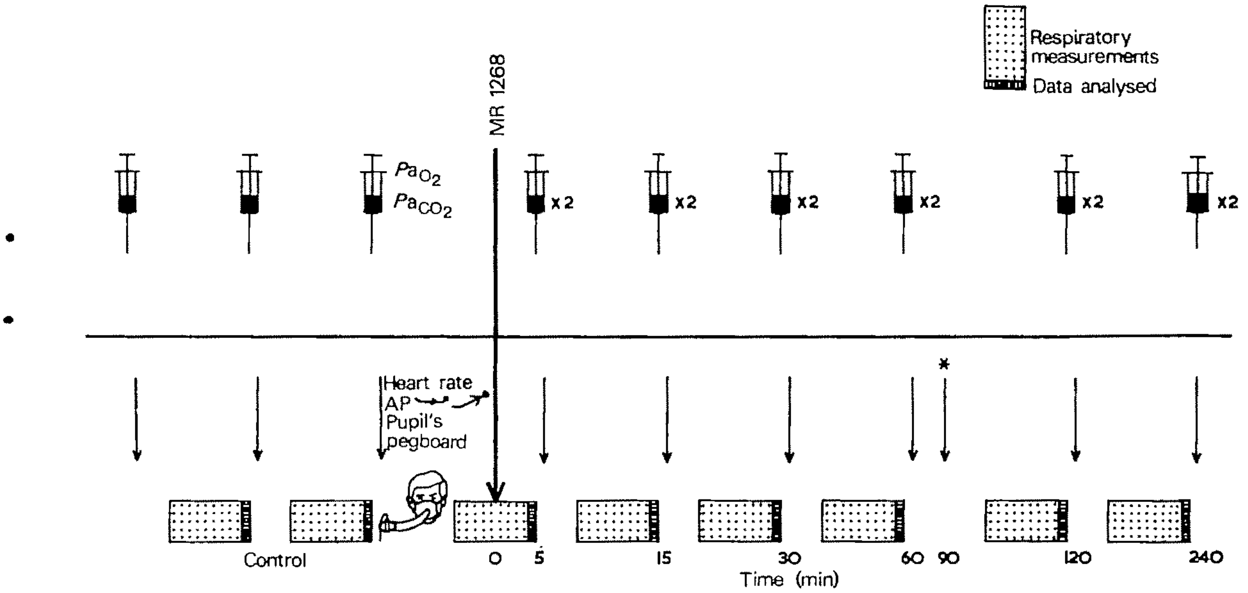

FIG. 2. Sequence of measurements. * Pegboard only.

Cardiovascular measurements. Systolic and diastolic arterial pressures were measured with an oscillotonometer, the same apparatus being used in all the subjects and all observations were made by one observer. With the 20-mg dose, percutaneous radial artery cannulation was performed under local anaesthesia before commencing the study to measure the changes in Pa_{CO_2} and Pa_{O_2}. The cannula also provided an opportunity to record arterial pressure continuously by connecting it to a pen recorder (Washington 400 MD/2) via a light weight transducer (Gaeltec Luer).

Measurements of arterial pressure were made in the recumbent and in the reverse Trendelenberg position (40° head-up tilt) to detect the possible occurrence of postural hypotension after the administration of MR 1268. Three control readings were taken at 10-min intervals during the period before the administration of the drug and mean values calculated.

Precordial e.c.g. electrodes were applied and a continuous record obtained through the study. Heart rate was calculated from the e.c.g. tracing.

Respiratory measurements. A previously calibrated pneumotachograph (Electrospirometer CS6; Mercury Electronics Ltd) measured the respiratory indices, which were displayed on a pen recorder. Although measurements of respiratory rate and minute volume were obtained throughout the 10-min period, only the results obtained during the final minute of each period were analysed (fig. 2).

When MR 1268 20 mg was given, 1 ml of arterial blood was withdrawn in a previously heparinized syringe at the intervals shown in figure 2 and analysed immediately for Pa_{CO_2} and Pa_{O_2} using an IL 400 blood-gas analyser (Instrumentation Laboratories Ltd).

Soporific effect. The degree of drowsiness was assessed periodically and graded by the observer as: 0 = fully awake; 1 = slight drowsiness; 2 = moderate drowsiness; 3 = extremely drowsy but easily roused; 4 = asleep.

Peg-board performance test. The time taken to transfer six pegs from one side of the board to the other was noted (Carson, 1975) before the administration of the drug, the mean of three tests being taken as the control. The subjects attempted the test at 5, 15 and 30 min after the injection of MR 1268 and at 30-min intervals until the "control" result was attained again.

Pupillary size and reaction. A National Heart Hospital pupil gauge (MIE) was held in front of the eye and the size of the pupil was matched against the appropriate perforation of a known diameter on the gauge. These measurements were made under standard lighting conditions and again when a beam of light was shone on the eye.

Subjective effects. The occurrence of the following side-effects was classified in a standardized interview: pain on injection, dry mouth, dizziness, euphoria, hallucinations, dreams or any other subjective effects. The occurrence of sweating during the study was recorded.

In this investigation each subject acted as his own control and the paired data were analysed by the Student's *t* test, average and standard error of the mean being given in the tables.

RESULTS

Cardiovascular measurements. The changes in mean arterial pressure were small and not statistically significant (table I). There was no evidence of postural hypotension with a 40° head-up tilt in any of the subjects.

A slight but statistically significant decrease in mean heart rate was observed with all four doses of MR 1268 (table II) ($P < 0.05$ to < 0.001). The maximum decrease occurred 30 min following the 10-mg dose.

Respiratory measurements. Respiratory frequency was practically unaltered after all four doses of MR 1268 (table III). Small changes in either direction were not significant.

An increase in average minute volume occurred after MR 1268 2.5 mg, but consistent decreases were noted following the 5-, 10- and 20-mg doses

TABLE I. *Mean arterial pressure (mm Hg ± SEM) at intervals following MR 1268 2.5, 5, 10 and 20 mg i.v.*

Dose (mg)	Control	Time after injection (min)					
		5	15	30	60	120	240
Recumbent							
2.5	94±1.1	94±1.3	90±1.8	90±2.0	96±2.0	96±2.0	96±2.0
5	94±1.0	91±1.7	91±1.4	93±1.8	92±1.4	94±0.9	93±0.8
10	93±2.0	92±3.3	95±4.5	94±3.2	96±3.9	96±2.2	93±2.2
20	88±2.0	87±4.5	87±3.1	86±3.0	90±3.2	89±2.9	89±2.7
Head-up							
2.5	98±1.1	98±2.0	92±1.9	92±1.8	90±1.9	89±1.8	89±2.5
5	90±1.4	87±2.2	86±1.5	88±1.3	88±2.2	88±2.4	88±2.3
10	94±2.2	92±3.3	92±3.3	93±3.0	96±1.6	95±1.0	93±1.7
20	85±2.3	85±2.6	85±2.1	87±2.2	87±2.6	89±1.9	88±2.0

TABLE II. *Average (± SEM) heart rate at intervals following MR 1268 2.5, 5, 10 and 20 mg i.v. (recumbent)*

Dose (mg)	Control	Time after injection (min)					
		5	15	30	60	120	240
2.5	72±4.4	70±4.2	68±4.4	67±3.9	66±4.5	66±4.5	69±4.2
5	73±5.2	69±3.9	67±4.5	67±4.7	65±5.0	66±4.6	65±4.4
10	74±4.1	68±3.1	66±3.6	64±4.0	64±3.8	64±3.3	64±3.1
20	72±4.1	68±3.5	68±3.6	66±3.3	69±3.0	63±2.7	64±2.4

TABLE III. *Changes in average respiratory frequency* (*b.p.m.* ± SEM) after MR 1268 2.5, 5, 10 and 20 mg

Dose (mg)	Control	Time (min) 5	15	30	60	120	240
2.5	13.2 ±3.31	13.2	12.8	12.7	13.7	13.2	12.0
5	12.3 ±2.73	11.3	12.0	10.7	12.2	11.7	11.7
10	11.7 ±1.86	11.7	11.0	11.3	11.5	9.8	9.7
20	12.0 ±2.10	13.7	13.3	12.3	13.3	13.0	12.3

(table IV; fig. 3). The maximum decreases in mean minute volume following 5 mg (16% of control; $P<0.001$) and 10 mg (26% of control; $P<0.001$) occurred 15 min after the injection of the drug. The maximum decrease in minute volume to 40% of control ($P<0.005$) occurred within 5 min of the administration i.v. of MR 1268 20 mg.

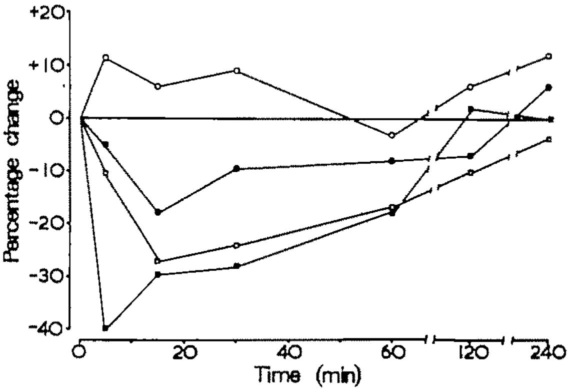

FIG. 3. Percentage change in average minute ventilation ($\dot{V}_E$) following MR 1268 2.5 mg (○), 5 mg (●), 10 mg (□) and 20 mg (■) i.v.

Pa_{CO_2}. Each value shown against individual subjects in table V represents an average of two or three measurements. Following MR 1268 20 mg, five of six subjects studied showed an increase of greater than 0.7 kPa at 5 min ($P<0.001$). At 15 min, Pa_{CO_2} remained increased significantly ($P<0.001$). At 15 min, Pa_{CO_2} remained increased significantly ($P<0.001$) the average increase being 0.5 kPa above baseline; at 30 min the average increase was 0.4 kPa ($P<0.001$). At 60 min, however, only one subject (No. 2) showed a sustained increase of Pa_{CO_2} greater than 0.7 kPa, while the others showed negligible increases which were not significant.

TABLE V. *Changes in* Pa_{CO_2} *(kPa) following MR 1268 20 mg i.v.*

Subjects	Control	Time (min) 5	15	30	60	120	240
1	5.6	6.3	6.1	5.8	5.8	5.7	5.7
2	5.4	6.2	6.2	6.2	6.1	5.3	5.2
3	5.1	5.8	5.7	5.9	5.5	5.4	5.3
4	5.2	6.0	5.6	5.7	5.8	5.5	5.3
5	5.5	6.3	6.0	5.5	5.2	4.8	5.0
6	5.6	6.0	5.8	5.8	5.7	5.7	5.7
Mean	5.4	6.1	5.9	5.8	5.7	5.4	5.4
±SEM	0.09	0.08	0.09	0.09	0.14	0.14	0.11
P		<0.001	<0.001	<0.001	n.s	n.s	n.s.

Pa_{O_2}. For technical reasons it was possible to report Pa_{O_2} changes in only five subjects (table VI). Individual findings given in table VI are based on an average of two to three measurements. The average resting Pa_{O_2} of 12.5kPa (range 12.1–12.9) was well within the normal physiological limits. Following MR 1268 20 mg there was a variable decrease; at 5 min the average decrease of 1.1 kPa

TABLE IV. *Changes in average minute volume (litre min*$^{-1}$ *± SEM) following MR 1268 2.5, 5, 10 and 20 mg.* *P<0.05; **P<0.01; ***P<0.001

Dose (mg)	Control	Time (min) 5	15	30	60	120	240
2.5	12.0 ±0.40	13.4 ±0.71	12.7 ±0.60	13.0 ±0.97	11.5 ±0.98	12.7 ±1.42	13.5 ±1.33
5	9.2 ±0.44	8.9 ±0.73	7.7 ±0.81***	8.3 ±0.26*	8.6 ±0.95	8.6 ±0.46	9.8 ±0.46
10	8.1 ±0.51	7.3 ±1.45	6.0 ±1.11***	6.1 ±1.77**	6.8 ±1.66*	7.4 ±1.85	8.7 ±0.40
20	8.6 ±0.08	5.2 ±0.97**	6.1 ±0.31***	6.2 ±0.42***	7.1 ±0.24***	9.0 ±0.44	8.6 ±0.50

TABLE VI. *Changes in* Pa_{O_2} *(kPa) following MR 1268 20 mg i.v.*

Subjects	Control	Time (min)					
		5	15	30	60	120	240
1	12.9	10.5	11.7	12.6	12.9	12.6	12.8
2	12.1	11.4	10.8	11.2	11.7	12.4	13.2
3	12.1	11.2	10.8	12.0	12.0	12.0	12.2
4	12.4	11.1	11.2	12.3	12.7	12.7	12.4
5	12.9	12.8	11.3	12.2	12.4	12.9	13.0
Mean	12.5	11.4	11.2	12.1	12.3	12.5	12.7
±SEM	0.8	0.38	0.17	0.24	0.22	0.15	0.19
P		<0.025	<0.001	n.s.	n.s.	n.s.	n.s.

(range 0.1–2.4) was significant ($P < 0.025$). More consistent decreases were seen at 10 min (average decrease = 1.3 kPa (range 1.2–1.6) ($P < 0.001$)).

Soporific effect. Subjects appeared to be unaffected by MR 1268 2.5 and 5 mg (fig. 4). With the 10-mg dose, five out of six subjects were slightly drowsy (at 5 and 15 min), the other being unaffected. All had recovered completely by 60 min. Following MR 1268 20 mg, one subject was moderately drowsy and the rest only slightly drowsy 5 min after injection. By 30 min, the soporific effects had begun to wane, although slight drowsiness persisted for up to 90 min in three of the subjects. All had recovered fully by 120 min. The most significant observation was that subjects seemed to emerge from the varying periods of sedation rather abruptly, exhibiting a clear-cut end point.

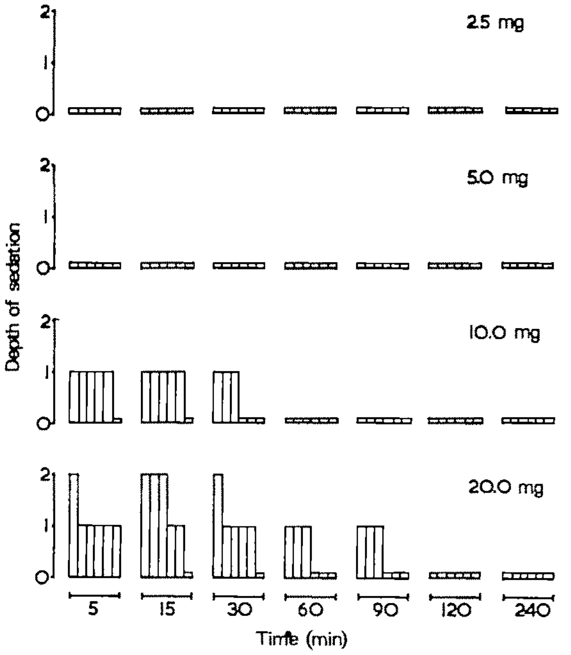

FIG. 4. Serial histograms showing depth of sedation with four different doses of MR 1268. Each block represents an individual subject. 0 = no sedation; 1 = slight drowsiness; 2 = moderate drowsiness.

The ability to undertake the peg-board performance test remained unchanged after MR 1268 2.5 mg. Following 5, 10 and 20 mg the time taken to return to pre-injection performance increased proportionately (fig. 5).

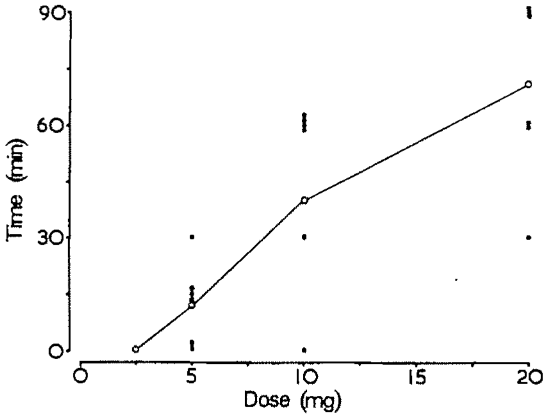

FIG. 5. Time (min) from injection to return of peg-board performance to control following different doses of MR 1268 i.v. ● = individual subject; ○ = mean value.

Pupillary size and reaction to light. These remained unchanged with all doses of MR 1268. The average pupillary diameter was 5 mm under standard room light, which decreased to 3 mm when a beam of light was shone towards the eyes. The reaction remained brisk and unaffected by the drug.

Subjective effects. Three of the six subjects studied reported a sensation of generalized warmth spreading all over the body within a few seconds of the injection. A "pleasant feeling" lasting for about 10 min followed the 10- and 20-mg doses of MR 1268 in two subjects. Apart from these, no other subjective effects were noticed.

DISCUSSION

The effect of a potent analgesic in a group of healthy, pain free, human volunteers may not truly represent the response from a group of patients in severe pain. Nevertheless, such studies do have a place in the initial investigation of a drug as they provide valuable information unobtainable from animal experiments and they demonstrate the general trends in the likely pharmacological response in patients.

There were no noteworthy changes in cardiovascular variables following MR 1268. The slight decrease in heart rate bore no relationship to the dose of the drug and was most probably a result of physical and mental relaxation.

The lack of significant changes in respiratory rate is notable, in view of the fact that this is often taken as an index of respiratory depression. Following MR 1268 2.5 mg, small increases in minute volume were noticed. This response was totally different from the consistent decreases subsequently seen with higher doses and it could be a result of conscious overbreathing on first exposure to the apparatus. It supports the original supposition that 2.5 mg is a "no-effect dose", at least in terms of respiratory depression, and the inclusion of this low dose was the reason for omission of a placebo in the study. Following MR 1268 5, 10 and 20 mg a much clearer trend emerged and decreases in minute volume seen were not only significant but also dose-related.

It is difficult to draw any firm conclusions from the changes in respiratory indices, particularly since a decrease in ventilation alone does not necessarily indicate respiratory depression. Jennet, Barker and Forrest (1968) have shown that potent analgesics such as morphine, phenoperidine and pentazocine reduce the basal metabolic rate with inevitable alterations in the respiratory pattern. Also, Bellville and his colleagues (1959) have observed that natural sleep *per se* can affect the respiratory indices and, when this effect cannot be separated from the true drug effect, it must be taken into account in assessing the extent of respiratory depression.

It is claimed that an increase in $P\text{CO}_2$ in subjects breathing room air, is a reliable index of "true" respiratory depression (Jennett, Barker and Forrest, 1968). In the present study, following MR 1268 20 mg, all subjects with one exception showed an increase in Pa_{CO_2} of the order of 0.7 kPa or more, within 5 min of the i.v. injection. Although these increases were not large, the consistency with which they occurred is significant, and they coincided with the maximum decreases in ventilation. Pa_{CO_2} remained increased significantly for up to 30 min. Changes in Pa_{O_2} were small and inconsistent. Although Pa_{O_2} is expected to decrease as Pa_{CO_2} increases, this can be altered by factors other than those causing respiratory depression and is not a useful criterion.

Like other opiates, MR 1268 would seem to produce dose-related drowsiness, but this was of short duration and only significant with 20 mg. Although the peg-board test may not be an ideal method of assessing recovery, it is simple to use and reproducible in its findings (Vickers, 1965; Carson, 1975). Apart from 2.5 mg, which had no effect, all other doses of MR 1268 (5, 10 and 20 mg) decreased the subjects' ability to undertake the peg-board performance test. As a result, the time taken to return to pre-injection performance increased with increasing dose.

Slight meiosis was reported following MR 1268 20–30 mg s.c. in a previous study involving three healthy volunteers; reaction to light remained uninhibited (J. H. Shelley, personal communication).

Sweating was the commonest side-effect reported to have occurred with a dose as low as 5 mg in both volunteers and patients during the studies undertaken in West Germany. After 20–30 mg s.c. mild vertigo and poor concentration followed by apathy and nightmares were reported in a small number of subjects. None of these side-effects was experienced by any of the subjects in the present study.

ACKNOWLEDGEMENTS

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EFFET D'UN NOUVEL ANALGESIQUE, MR 1268, SUR LES INDICES CIRCULATOIRES ET RESPIRATOIRES DE VOLONTAIRES

RESUME

Le MR 1268 est un dérivé du benzmorphane qui a des propriétés ressemblant nettement à celles de la morphine, mais dont les propriétés antagonistes sont plus faibles. Il a été administré à six hommes volontaires en bonne santé, chacun ayant reçu 2,5; 5; 10 et 20 mg de MR 1268 administrés au hasard. Il n'y a pas eu de changements significatifs dans les indices cardiovasculaires mesurés. On a cependant remarqué une diminution significative et liée à la dose dans le débit cardiaque à l'expiration. Avec 20 mg, les augmentations uniformes de la Pa_{CO_2} ont coïncidé avec une diminution maximale de la ventilation, montrant un certain degré d'hypoventilation alvéolaire. L'assoupissement a été lié à la dose, mais celui-ci a été de courte durée et n'a été significatif qu'avec la dose de 20 mg. La dimension et la réaction des pupilles n'ont pas été affectées.

AUSWIRKUNG EINES NEUEN SCHMERZLINDERUNGSMITTELS (MR 1268) AUF KREISLAUF- UND ATMUNGSINDIZIEN

ZUSAMMENFASSUNG

MR 1268, ein Benzmorphan-Derivat mit ausgeprägten morphium-ähnlichen Eigenschaften und schwächeren Gegenwirkungseingenschaften, wurde bei sechs gesunden männlichen Freiwilligen verabreicht, von den jeder 2,5, 5, 10 und 20 mg MR 1268 in wahlloser Folge intravenös bekam. Es wurden keine bedeutende Änderungen der gemessenen kardiovaskulären Indizien festgestellt. Es wurden jedoch bedeutende dosisbezogene Verringerungen des expirierten Minutenvolumens festgestellt. Bei 20 mg trafen wiederholte Steigerungen der Pa_{CO_2} mit maximaler Verminderung der Ventilation zusammen, was einen gewissen Grad von alveolärer Hypoventilation andeutet. Schläfrigkeit wär dosisbezogen aber von kurzer Dauer, und nur bei 20 mg bedeutend. Grösse und Reaktion der Pupillen blieben unverändert.

EFECTO DE UN NUEVO ANALGESICO, EL MR 1268, SOBRE LOS INDICES CIRCULATORIOS Y RESPIRATORIOS DE VOLUNTARIOS

SUMARIO

El MR 1268 es un derivado benzomorfínico con propiedades marcadamente similares a las de la morfina y con propiedades antérgicas más debiles. Este analgésico se administró a seis hombres sanos y voluntarios, recibiendo cada uno de ellos 2,5, 5, 10 y 20 mg de MR 1268 al azar. No se presentaron cambios significativos en los índices cardiovasculares medidos. Sin embargo, se observaron disminuciones significativas y relacionadas con la dosis en el volumen diminuto espirado. Con 20 mg se presentaron incrementos consistentes en Pa_{CO_2} los cuales coincidieron con la disminución máxima de la ventilación, indicando así cierto grado de hipoventilación alveolar. La somnolencia vino en función de la dosis pero fue de corta duración y sólo fue significativa con 20 mg. El tamaño y la reacción de las pupilas no quedó afectado.

Br. J. Anaesth. (1981), 53, 1337

STEADY-STATE PLASMA FENTANYL IN THE RABBIT*

J. R. A. RIGG, T. Y. WONG, P. HORSEWOOD AND J. R. HEWSON

SUMMARY

Linear pharmacokinetic models were obtained for fentanyl in anaesthetized rabbits. A composite model was used to predict the bolus dose and infusion rates necessary to achieve rapidly a steady-state concentration of fentanyl in plasma. When this was tested in a further six rabbits, steady-state concentrations were greater than predicted. The most likely reasons for this are imperfect mixing between plasma and the central compartment, and substantial uptake of fentanyl by the lung. These sources of error were allowed for in modifications to the model. On further testing, a 4-h infusion set to achieve a plasma fentanyl concentration of 10 ng ml^{-1} yielded actual concentrations ranging from a mean low of 8.7 ng ml^{-1} to a mean high of 18.0 ng ml^{-1}. The second model described more precisely the disposition of fentanyl, although a tendency to overestimate dosing requirement remained. This tendency is probably a consequence of continuing lung uptake of fentanyl. The demonstrated ability to obtain rapidly and maintain for 4 h "steady" blood fentanyl concentrations suggests that the method merits further investigation with other drugs both in animals and man.

In an accompanying paper, the theory of a general method to obtain rapidly and maintain indefinitely a steady plasma drug concentration is described (Rigg and Wong, 1981). The present paper describes experiments to test the reliability of the method when used to obtain steady concentrations of plasma fentanyl in the anaesthetized rabbit.

The method uses pharmacokinetic indices derived from studies of the disposition of the drug to calculate a loading bolus dose and a series of two or three different, consecutive, constant rate infusions to achieve, as rapidly as possible, a specified plasma concentration and to maintain this within predetermined limits. For most drugs, the decay of plasma concentration with time, following an i.v. injection, is a first-order process; that is, one in which rate of decay of concentration is a function of concentration. Most commonly, the concentration–time profile is described adequately by the biexponential expression $C_P = A\,e^{-\alpha t} + B\,e^{-\beta t}$, where C_P = plasma concentration, t = time, A and B are intercept and α and β slope indices of the semi-logarithmic plot of C_P and t (Greenblatt and Koch-Weser, 1975). In the present work, indices derived from studies of fentanyl disposition in anaesthetized rabbits were used to predict infusion regimens for different fentanyl steady-state concentrations.

Fentanyl was chosen for study for several reasons. First, it is a narcotic widely used in anaesthesia and neuroleptanalgesia. Second, there is increasing clinical and experimental evidence of prolonged and toxic effects following multiple doses (Schleimer et al., 1978; Hug and Murphy, 1979; McQuay et al., 1979; Murphy, Olson and Hug, 1979). Third, a highly specific and sensitive radioimmunoassay (RIA) is available to measure fentanyl in plasma (Henderson et al., 1975; Schleimer et al., 1978).

METHODS

Pharmacokinetic parameters describing fentanyl disposition were determined experimentally and used to test a method of achieving rapidly and maintaining indefinitely steady-state plasma fentanyl concentration in anaesthetized rabbits (Rigg and Wong, 1981).

Fentanyl was administered i.v. to six anaesthetized rabbits (series A) and serial blood samples taken to characterize fentanyl disposition for 3 h following the injection. Results were analysed to

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calculate values of standard pharmacokinetic indices representative of this group of experimental animals (Greenblatt and Koch-Weser, 1975). These indices were used to calculate an infusion regimen predicted to provide, as rapidly as possible, steady-state plasma fentanyl concentrations in a similar group of experimental animals (Rigg and Wong, 1981). This regimen was applied to a second group of six anaesthetized rabbits (series B) and the plasma fentanyl time profile determined. The failure of this regimen to predict plasma fentanyl as precisely as expected was examined from two standpoints: the precision of mathematical methods for characterizing a representative concentration–time profile, and the validity of assumptions of the mathematical model of the pharmacokinetic system. It was thought that the 1- and 2-min samples following the original rabbit fentanyl administrations were invalid because of imperfect mixing of drug in the central compartment and substantial first-pass drug uptake by the lung (Hess, Herz and Friedel, 1971). Accordingly, the results of series A experiments were analysed with the suspect values omitted and pharmacokinetic indices redetermined. From these indices a revised infusion regimen was calculated. This regimen was tested in a further group of five rabbits and the concentration–time profile determined (series C).

EXPERIMENTAL PROCEDURE

Series A

Six New Zealand white rabbits, weighing from 2.67 to 3.13 kg, were studied. Each was anaesthetized with i.v. sodium pentobarbitone and the left internal jugular vein and right common carotid artery cannulated. Anaesthesia was maintained with increments of sodium pentobarbitone as required and ventilation of the lungs maintained with a Harvard small animal pump ventilator, using a gas mixture of 50% nitrous oxide in oxygen via a tracheostomy. Ventilation and acid–base status were maintained within normal limits, with frequent arterial blood-gas analysis using a Radiometer BMS3 blood-gas analyser. Intravenous normal saline 20–40 ml h^{-1} was given to replace blood loss from sampling and to maintain adequate hydration. Each rabbit was given fentanyl citrate 100 µg kg^{-1} as an infusion of 4 min duration. Blood samples were taken before (control) and at 1, 2, 3, 4, 6, 8, 10, 15, 20, 30, 60, 90, 120 and 180 min after the infusion. Samples were allowed to clot, spun down to yield serum and maintained at 4 °C until analysed for total serum fentanyl concentration by RIA.

Serum fentanyl disposition was determined by non-linear least squares regression (BMDP, 1977), with appropriate correction for the 4-min infusion (Loo and Riegelman, 1970). Different pharmacokinetic models were tested using the statistical method described by Boxenbaum, Riegelman and Elashoff (1974) to determine the simplest model that described a post-infusion fentanyl concentration–time curve representative of the group, and for the curves of individual rabbits. The group indices were used to predict dosage regimens to achieve rapidly and maintain steady-state plasma fentanyl concentrations (C_P^{ss}) ranging from 10 to 200 ng ml^{-1} with a predicted limit of deviation of 10% or less of C_P^{ss} (Vaughan and Tucker, 1976; Rigg and Wong, 1981).

This regimen was tested in two ways. First, the dosage regimen was tested by computer simulation; the infusion regimen (based upon group results) was applied to six hypothetical rabbits having pharmacokinetic indices identical to those of the six rabbits whose individual dispositions had been determined. Second, the dosage regimen predicted to provide a plasma concentration of 10 ng ml^{-1} was given to six additional anaesthetized rabbits (series B).

Series B

Six New Zealand white rabbits, weighing 2.90–4.00 kg were studied. Each rabbit was anaesthetized, the tracheostomy, cannulation, ventilation, monitoring and infusion with saline being the same as in series A animals. Each was given a bolus and three consecutive constant-rate (zero order) infusions: from 0 to 40, 40 to 120 and 120 to 240 min, in doses predicted to provide C_P^{ss} fentanyl 10 ng ml^{-1} ± 10%. Blood samples were taken before the bolus dose was given and at 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150, 180, 210, 245, 250, 255, 260, 270, 280 and 300 min. Samples were allowed to clot, spun down and serum stored at 4 °C until analysis of total serum fentanyl by RIA.

The results of the series B experiments were, unexpectedly, substantially higher than predicted. The pharmacokinetic model assumes, *inter alia*, that there is instantaneous perfect mixing of the drug in the central compartment and negligible lung uptake. If these assumptions are not valid, the 1- and 2-min samples may not be truly representative of central compartment concentrations. To test this possibility, the series A results were re-analysed, omitting these data points. This changed the analysis to the extent that fentanyl disposition was more adequately described by a three-compartment than by a two-compartment system (Boxenbaum, Riegelman and Elashoff, 1974). Accordingly, the recalculated parameters were used to predict a new dosage schedule to achieve rapidly and maintain fentanyl C_P^{ss} of $10\,\mathrm{ng\,ml^{-1}}$ $\pm 20\%$. This regimen was tested in a further group of five anaesthetized rabbits (series C).

Series C

Five New Zealand white rabbits weighing from 2.64 to 3.57 kg were studied, using the same experimental procedure as in the series A and B experiments. Each rabbit was given a bolus of fentanyl $5.24\,\mu\mathrm{g\,kg^{-1}}$ over 3–5 s followed by $1.00\,\mu\mathrm{g\,kg^{-1}\,min^{-1}}$ from 0 to 90 min and $0.48\,\mu\mathrm{g\,kg^{-1}\,min^{-1}}$ from 90 to 240 min. Blood samples were taken, allowed to clot, spun down and analysed in the same way as in the series B experiments.

FENTANYL ASSAY

Antiserum was raised in rabbits using carboxyfentanyl coupled to bovine serum albumin and was prepared by the procedure of Henderson and others (1975) but modified such that the reduction of the intermediate imine was done with "vitride" (Eastman Organic Chemicals). Tritiated fentanyl was synthesized by the simple and novel route described, giving a product of much higher specific activity than previously reported.

Preparation of ^{3}H-fentanyl

4-Anilino-1-(β-phenethyl) piperidine (140 mg), synthesized as an intermediate in the carboxyfentanyl preparation, was dissolved in dry benzene 2 ml and acrylyl chloride 50 µlitre was added. A precipitate formed immediately and after 1 h water 1 ml was added, followed by saturated sodium bicarbonate solution 3 ml. The product was extracted into ether (3 × 5 ml); the combined organic phases after drying and evaporation gave a pale yellow crystalline solid which was recrystallized from cyclohexane yielding colourless needles of N-(1-phenethyl-4-piperidinyl)-N-phenylpropenamide, m.p. 108–109° (143 mg). Hydrogenation of the propenamide derivative at atmospheric pressure using a 5% palladium on charcoal catalyst gave fentanyl having characteristics identical to those previously reported by Henderson and others (1975). A sample of the propenamide derivative was sent for catalytic tritiation (Amersham Corp., Tritium Labelling Service); the resulting tritiated fentanyl had a nominal specific activity of $35\,\mathrm{Ci\,mmol^{-1}}$. Residual exchangeable tritium was removed by three cycles of acid–base extraction and the exchanged material stored at 4 °C in saline containing ethanol (10% v/v).

Radioimmunoassay

Rabbit serum 25 µlitre was introduced into small centrifuge tubes followed by tritiated fentanyl 25 µlitre (about 12 000 c.p.m.) and acetate buffer 50 µlitre, pH 4.7. Antifentanyl antiserum 100 µlitre, diluted 1/4000 with 1/200 normal rabbit serum was added and the tubes were left in the dark at room temperature for 18 h. Saturated ammonium sulphate solution 200 µlitre was added and after 15 min at room temperature precipitated protein was sedimented by centrifugation for 3 min at 8000 *g*). A 100-µlitre aliquot of the supernatant was removed and introduced into a counting vial containing 1 ml of water; counting fluid was added and radioactivity determined.

A standard curve was constructed using normal rabbit serum in place of fentanyl containing serum and using buffer containing known amounts of fentanyl in place of normal buffer. Maximum binding of ^{3}H-fentanyl in the assay was carried out as for the standard curve but using buffer containing no fentanyl. Previous titration of the antiserum under these latter conditions has shown about 50% binding for a 1/4000 dilution. Background binding was determined by replacing the antiserum with 1/200 normal rabbit serum and this radioactivity was subtracted from all tubes. All samples were run in duplicate.

The standard curve covered the range 0–666 pg of added ligand per tube and from initial data, plots of normalized percent bound (B/Bo × 100) *v.* log amount of added ligand showed a linear portion covering the range 50–500 pg per tube. When necessary, unknown samples were diluted with normal serum to fall within this range. Subsequently data were analysed using a Scatchard plot obtained with a Wang 600 table-top computer.

Specificity of antisera

Specificity of the antisera was determined by constructing standard curves as above and assessing the ability of increasing amounts of test compounds to compete with tritiated fentanyl for antifentanyl binding sites. Compounds so tested were: carboxyfentanyl, fentanyl, droperidol, morphine and 4-anilino-1-(β-phenethyl) piperidine, a major metabolite of fentanyl in rats. Results showed the antisera to be specific; carboxyfentanyl, the hapten used for immunization, was the only compound tested to show any significant inhibition.

RESULTS

Series A

Results of all plasma fentanyl analyses are given in table I. All individual rabbit plasma fentanyl time curves and the pooled results were described adequately by a two-compartment system. The equations fitted to individual and pooled results are given in table II and the corresponding disposition curves shown in figure 1. The following dose regimen was calculated to provide a steady

TABLE II. *Fentanyl doses and biexponential expressions ($C_P = Ae^{-\alpha t} + Be^{-\beta t}$) describing plasma fentanyl concentration–time curves of series A individual rabbits and pooled results as determined by the method of Boxenbaum, Riegelman and Elashoff (1974). C_P = plasma concentration (ng ml^{-1}), and t = time (h)*

Rabbit no.	Dose (µg)	C_P
2	286	$120.9\,e^{-16.2t}+5.6\,e^{-0.336t}$
3	268	$127.9\,e^{-17.4t}+5.5\,e^{-0.312t}$
4	284	$81.2\,e^{-11.4t}+5.7\,e^{-0.378t}$
5	285	$216.4\,e^{-12.6t}+7.8\,e^{-0.342t}$
6	313	$77.2\,e^{-16.2t}+7.2\,e^{-0.468t}$
7	296	$126.4\,e^{-12.6t}+7.8\,e^{-0.426t}$
Pooled		$113.0\,e^{-12.0t}-6.0\,e^{-0.318t}$

TABLE I. *Total plasma fentanyl (ng ml^{-1}) concentrations (± SEM) in six anaesthetized rabbits 1, 2, 3, 4, 6, 8, 10, 15, 20, 30, 60, 90, 120 and 180 min after 4 min infusion of fentanyl citrate*

Rabbit no.	Time after administration of fentanyl (min)													
	1	2	3	4	6	8	10	15	20	30	60	90	120	180
2	54.9	57.6	43.6	34.5	17.4	15.8	10.2	9.2	8.9	5.0	4.8	3.3	2.9	3.2
3	53.4	46.7	51.0	39.4	16.0	11.8	9.5	—	5.9	4.3	3.8	3.7	—	2.1
4	50.8	57.5	51.6	24.2	22.6	19.0	13.8	8.7	6.0	7.8	3.3	2.8	2.8	1.9
5	105.0	81.6	72.3	66.6	58.8	25.5	23.0	10.4	11.8	9.5	4.4	4.1	4.8	2.8
6	37.2	75.5	45.8	20.2	12.4	11.1	15.3	9.3	6.9	5.2	3.8	3.1	3.2	1.8
7	81.2	57.0	57.6	52.3	30.7	21.5	17.0	11.1	9.3	7.2	4.5	4.0	2.8	2.6
Mean	63.72	62.65	53.65	39.53	26.32	17.45	14.80	9.75	8.13	6.50	4.10	3.50	3.30	2.40
SEM	10.08	5.36	4.23	7.14	6.99	2.30	2.02	0.43	0.94	0.82	0.23	0.21	0.38	0.22
n	6	6	6	6	6	6	6	5	6	6	6	6	5	6

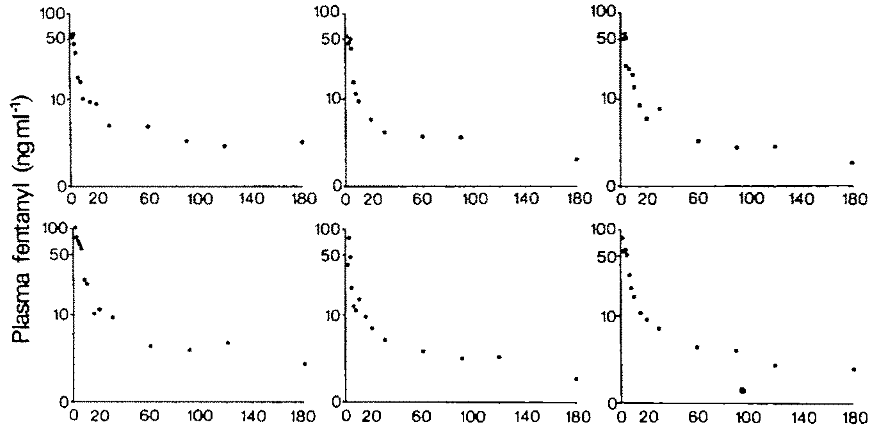

FIG. 1. Plasma fentanyl disposition in six anaesthetized rabbits (series A).

plasma fentanyl concentration of 10 ng ml^{-1}, using the indices of the biexponential expression derived from the pooled results: bolus (*X*d) 8.41 μg kg^{-1}; infusions: Q_1 1.33 μg kg^{-1} min^{-1}; Q_2 0.91 μg kg^{-1} min^{-1}; Q_3 0.59 μg kg^{-1} min^{-1}. The effect of giving this regimen to six hypothetical rabbits with disposition characteristics shown in table II was predicted by computer simulation. The predicted curves are shown in figure 2, together with the prediction for a rabbit with a disposition characteristic described by the pooled results.

Series B

When the above regimen was given to six more anaesthetized rabbits, plasma fentanyl concentrations ranged from a mean low of 13.8 ng ml^{-1} at 4 h to a mean high of 29.1 at 30 min. The greatest individual value was 53 ng ml^{-1} at 40 min and the smallest values were 3.5 ng ml^{-1} at 5 min and 10.7 ng ml^{-1} at 240 min. Mean values (± SEM) plotted for the 4-h infusion and for 1 h after infusion are shown in figure 3. These results indicate that the infusion regimen consistently over-estimated fentanyl dose requirements for

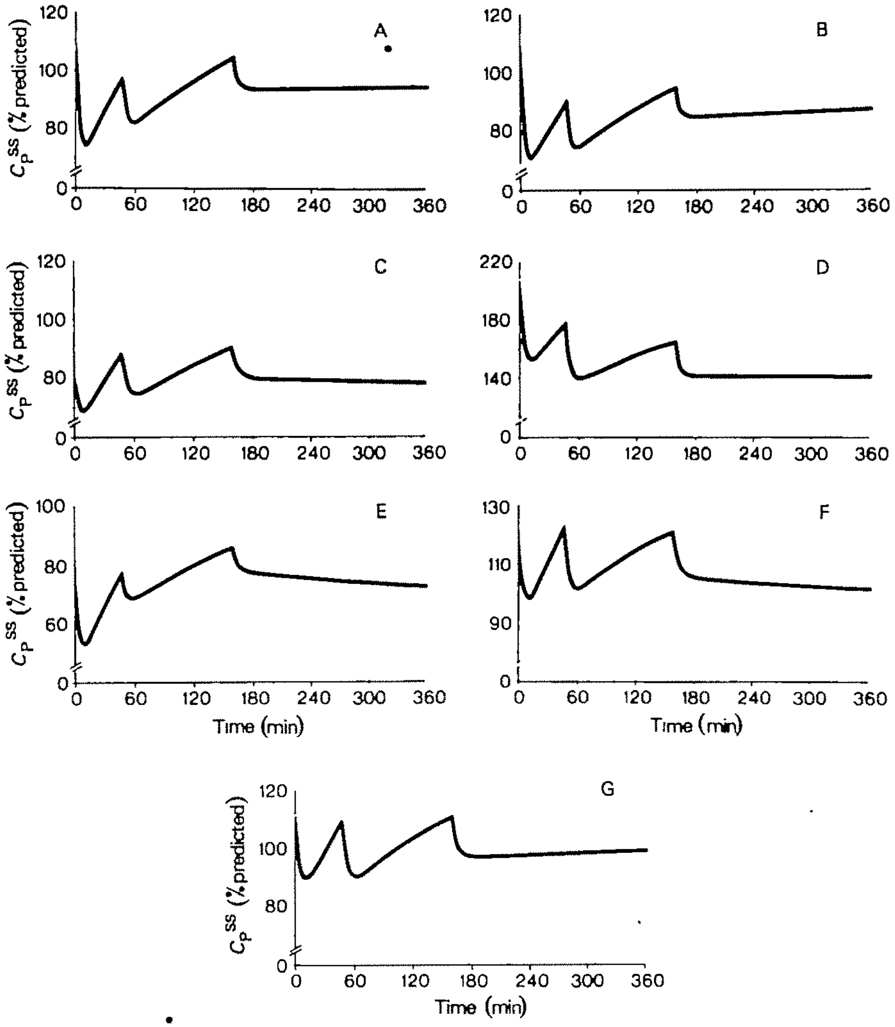

FIG. 2. Plasma fentanyl concentration–time profiles predicted by application of steady-state dose regimen to hypothetical rabbits (panels A–F), whose fentanyl disposition is described by the biexponential expressions given in table II and to a hypothetical rabbit with disposition characterized by the group data (panel G).

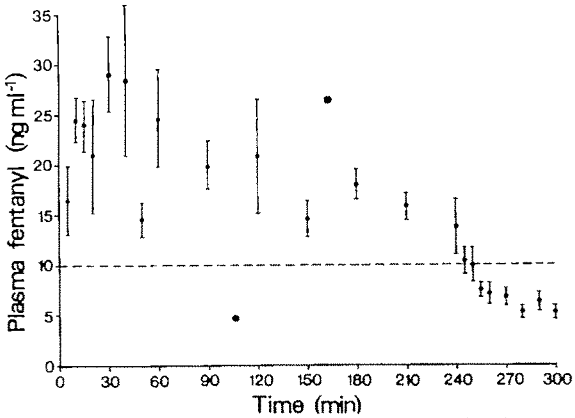

FIG. 3. Mean (± SEM) plasma fentanyl concentration from 0 to 300 min, during and after administration of steady-state dose regimen for 4 h, predicted to provide C_p^{ss} 10 ng ml^{-1} ± 10% (series B).

C_p^{ss} 10 ng ml^{-1}. As described in the methods section, the series A results were re-analysed, omitting 1- and 2-min plasma fentanyl concentration data points. With these values omitted, fentanyl disposition was more adequately described by a three-compartment system (Boxenbaum, Riegelman and Elashoff, 1974). The indices of this model were used to calculate the following regimen predicted to give C_p^{ss} fentanyl 10 ng ml^{-1} ± 20%: bolus 5.24 µg kg^{-1}; infusions Q_1 1.00 µg kg^{-1} min^{-1} from 0 to 90 min and Q_2 0.48 µg kg^{-1} min^{-1} from 90 min.

Series C

When this recalculated regimen was given to a further five anaesthetized rabbits, plasma fentanyl concentrations ranged from a mean low of 8.7 ng ml^{-1} at 4 h to a mean high of 18.0 ng ml^{-1} at 60 min. The greatest concentration observed in an individual rabbit was 22.8 ng ml^{-1} and the smallest was 5.0 ng ml^{-1} at 240 min. Individual rabbit concentration–time profiles and the mean values (± SEM) plotted for the 4-h infusion and for 1 h after infusion are shown in figure 4.

DISCUSSION

The objective of the present experiments was to test a method for obtaining rapidly a given steady-state plasma drug concentration and maintaining this within predetermined narrow limits, using i.v. fentanyl in the anaesthetized rabbit. Kruger-Thiemer (1968) pointed out that this objective would not be achieved rapidly (in less than 10 min) or safely (fluctuations of C_p less than 50% of C_p^{ss}) for drugs the disposition of which is characterized by a multi-compartment system, unless at least two or three different consecutive constant rate infusions are given following an i.v. loading dose. The work of Mitenko and Ogilvie (1972) and Wagner (1974) provide further evidence that either safety (Mitenko and Ogilvie, 1972) or speed of attainment of steady state (Wagner, 1974) must be sacrificed if only two dosing rates are used, a finding reaffirmed by our studies (Rigg and Wong, 1981). Accordingly, a modification of the method of Vaughan and Tucker (1976) was applied to the problem of obtaining rapidly and maintaining steady-state plasma fentanyl in the anaesthetized rabbit. A further objective of the experiments was to explore the general utility of using group data to predict steady-state blood concentrations in prospective animals or subjects. Consequently, the

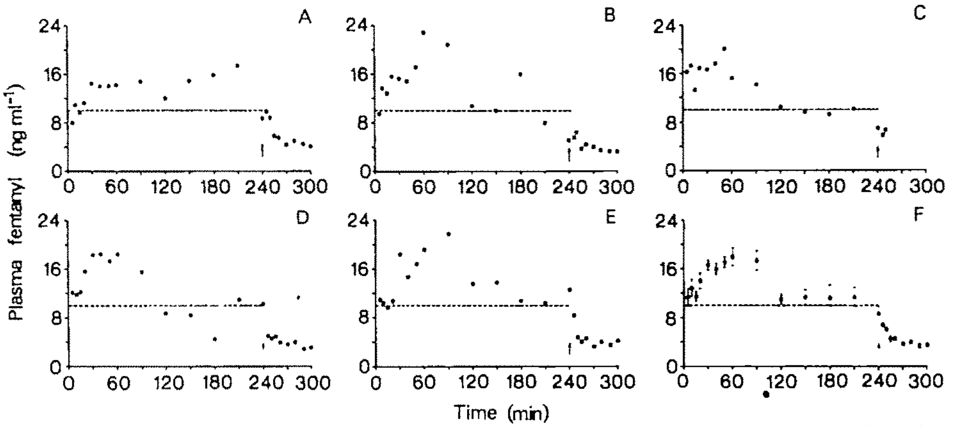

FIG. 4. Plasma fentanyl concentration–time profiles from 0 to 300 min obtained in five rabbits using recalculated dose regimen, for 4 h, predicted to provide C_p^{ss} 10 ng ml^{-1} ± 20% (series C, panels A–E) and mean (± SEM) plasma fentanyl concentration–time profile (panel F).

composite disposition of fentanyl from results obtained in six anaesthetized rabbits (series A) was used to determine a steady-state dose regimen. Considerable inter-individual variation in disposition was observed among these rabbits, such that computer predictions of steady-state fentanyl concentrations in individual rabbits showed fluctuations ranging from 53 to 207% of C_p^{ss} (fig. 2). When the dose regimen was applied experimentally to a further group of rabbits (series B), the plasma fentanyl concentrations were consistently greater than predicted (100 to 295%, fig. 3). However, inter-individual variation was of an order of magnitude comparable to the computer simulation curves.

Meffin and others (1979) pointed out that the ability to predict plasma concentrations during multiple dose regimens, using derived pharmacokinetic parameters as the basis of prediction, depends upon how precisely the derived parameters describe the true disposition of the drug.

A re-evaluation of individual plots of plasma fentanyl *v.* time (series A) resulted in a critical evaluation of the pharmacokinetic model. The initial bolus was given over 4 min and appropriate correction made for infusion time in determining disposition (Loo and Riegelman, 1970). However, all 1-min and some 2-min sample concentrations were considerably less than might be expected by extrapolating 3–10 min results back to the zero time point. This suggests that some assumptions of the open two-compartment model—that plasma is representative of the central compartment and that the drug is instantaneously mixed and homogeneously distributed throughout the central compartment—may not be valid. A further factor which may contribute to systematic underestimation of true central compartment concentration is the known predilection of the lung to take up fentanyl (Hess, Herz and Friedel, 1971).

The importance of this possible source of error lies in the importance of precise determination of the volume of the central compartment (V_1), in the calculation of the steady-state dose regimen. The volume of the central compartment is determined from the equation $V_1 = Xd/A+B$, where Xd is the bolus dose and $A+B$ is plasma concentration at zero time. If the sources of error enumerated above lead to an underestimate of $A+B$, V_1 will be overestimated. This will cause an overestimate of the dose requirements for a given C_p^{ss} value. Accordingly, the hypothesis that "non-representative plasma concentrations caused overestimation of V_1" was tested by re-analysing series A results, omitting 1- and 2-min data points. This altered the pharmacokinetic model markedly, such that the data were better described by a three-compartment system, with V_1 about 50% less than that of the first model.

The application to a third group of rabbits (series C) of another regimen, calculated from the revised pharmacokinetic indices, resulted in a closer approximation of the predicted steady-state value (100–170% C_p^{ss}), suggesting that the corrected model indices more precisely describe the true disposition of fentanyl (Meffin et al., 1979). However, series C results do show a similar but smaller tendency to systematic overestimation of dosing requirements. This suggests that the 3- and 4-min plasma concentrations may also underestimate true central compartment concentrations. Nevertheless, the ability to maintain a steady-state blood concentration within the range observed suggests that this general approach merits further investigation as a method of rapidly obtaining a desired steady-state concentration.

The method has the advantage that it is easily applied with a computer, so that the physician only has to make one decision—the choice of the desired steady state blood concentration. Experimentally, the method can be used, as in the present study, to examine the validity of a pharmacokinetic model and some of the assumptions upon which it is based. If the method functions as reliably for fentanyl as the present results indicate, more precise steady-state blood concentrations should be obtained with drugs that (a) are not as quickly distributed and redistributed; (b) are not taken up as avidly by the lung and (c) can be measured in biological fluids more precisely. The method has the potential to develop a general approach to steady-state dosing of all i.v. drugs used in anaesthesia, as well as in acute medical circumstances, when potentially toxic drugs must be given quickly yet safely.

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NOTE: The programme listing for the programme to compute infusion regimens from pharmacokinetic constants (VANDT) is available from the corresponding author.

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EQUILIBRE CINETIQUE DU FENTANYL DANS LE PLASMA CHEZ LE LAPIN

RESUME

Nous avons obtenu des modèles pharmacocinétiques linéaires pour le fentanyl chez des lapins anesthésiés. Nous avons utilisé un modèle composé pour prévoir la dose du bol et les taux de perfusion nécessaires pour atteindre rapidement un équilibre cinétique des concentrations de fentanyl dans le plasma. Lorsque celui-ci a été essayé sur six autres lapins, les concentrations d'équilibre cinétique ont été plus fortes que prévues. Les raisons les plus vraisemblables de cet état de choses sont: le mélange imparfait du plasma et du compartiment central ainsi qu'une importante fixation de fentanyl par le poumon. Nous avons tenu compte de ces sources d'erreur pour effectuer des modifications au modèle. Lorsqu'on a fait de nouveaux essais, une perfusion de 4 h conçue pour obtenir des concentrations de 10 ng ml^{-1} de fentanyl dans le plasma, a en fait donné des concentrations s'échelonnant entre une moyenne (basse) de 8,7 ng ml^{-1} et une moyenne (haute) de 18 ng ml^{-1}. Le second modèle décrit plus précisément la disposition du fentanyl, bien que l'on ait toujours tendance à surestimer le dosage. Cette tendance est probablement la conséquence de la continuation de la fixation de fentanyl dans le poumon. La possibilité d'obtenir rapidement et de maintenir pendant quatre heures des concentrations stables de fentanyl dans le sang, comme nous l'avons démontré, laisse penser que cette méthode mérite d'être étudiée en profondeur avec d'autres médicaments, aussi bien sur des animaux que sur des humains.

STATIONÄRES PLASMAFENTANYL BEIM KANINCHEN

ZUSAMMENFASSUNG

Es wurden lineare pharmakokinetische Modelle für Fentanyl bei anästhesierten Kaninchen aufgestellt. Ein zusammengesetztes Modell wurde verwendet, um die zur schnellen Herstellung einer stationären Konzentration von Fentanyl in Plasma notwendigen Bolus-Dosis und Infusionsgeschwindigkeiten vorauszusagen. Als dies bei sechs weiteren Kaninchen getestet wurde, hat es sich herausgestellt, dass die stationären Konzentrationen grösser waren, als vorausgesagt wurde. Als wahrscheinlichsten Gründe hierfür sind eine unvollkommene Mischung zwischen Plasma und dem zentralen Abteil und eine bedeutende Aufnahme von Fentanyl durch die Lunge anzusehen. Diese Fehlerquellen wurden durch Änderung des Modells berücksichtigt. Beim weiteren Testen hat eine 4-stündige Infusion, die eine Plasmafentanylkonzentration von 10 ng ml^{-1} bewirken sollte, tatsächliche Konzentrationen im Bereich von einem mittleren niedrigen Wert von 8,7 ng ml^{-1} bis zu einem mittleren hohen Wert von 18,0 ng ml^{-1} hervorgerufen. Das zweite Modell hat die Disposition von Fentanyl mit grösserer Genauigkeit beschrieben, obwohl eine Tendenz zur Überschätzung der Dosen weiterhin festzustellen war. Diese Tendez ist wahrscheinlich eine Folge der fortwährenden Aufnahme von Fentanyl durch die Lunge. Die erwiesene Fähigkeit, stationäre Blutfentanylkonzentrationen schnell zu erreichen und auch 4 Stunden lang aufrechtzuerhalten, deutet darauf hin, dass die Methode weitere Untersuchungen mit anderen Drogen, sowohl beim Menschen als auch bei Tieren, gerechtfertigen würde.

CONCENTRACION DE FENTANILO EN ESTADO DE REGIMEN EN EL PLASMA DEL CONEJO

SUMARIO

Se obtuvieron modelos farmacocinéticos lineales correspondientes al fentanilo en conejos anestesiados. Se usó un modelo compuesto para predecir la dosis del bolo y los regímenes de infusión necesarios para lograr rápidamente una concentración de fentanilo en estado de régimen en el plasma.

Cuando esto se verificó en otros seis conejos, las concentraciones en estado de régimen fueron más elevadas de lo previsto. Las causas más probables de esta característica son la mezcla imperfecta entre el plasma y el compartimiento central, así como una considerable admisión de fentanilo por parte del pulmón. Estas fuentes de error se tuvieron en cuenta en las modificaciones del modelo. En pruebas posteriores, una infusión de cuatro horas establecida para lograr una concentración de 10 ng ml^{-1} de fentanilo en el plasma, produjo concentraciones reales que oscilaron desde una media inferior de 8,7 ng ml^{-1} hasta una media superior de 18,0 ng ml^{-1}. El segundo modelo describió de forma más precisa la disposición del fentanilo, aunque permaneció una tendencia a sobreestimar la dosificación necesaria. Esta tendencia es, probablemente, una consecuencia de la continua admisión de fentanilo por parte del pulmón. La abilidad demostrada para obtener rápidamente y para mantener concentraciones de fentanilo en "estado de régimen" en la sangre por espacio de cuatro horas, sugiere que el método debiera investigarse en mayor profundidad con otras drogas, tanto en animales como en el hombre.

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PROLONGATION OF THE Q–T INTERVAL (ROMANO–WARD SYNDROME): ANAESTHETIC MANAGEMENT

J. PONTE AND J. LUND

SUMMARY

The anaesthetic management is described of a patient with prolonged Q–T interval which had been complicated by ventricular fibrillation at induction of general anaesthesia for a previous operation. This complication was prevented by effective premedication with i.v. propranolol and block of the left stellate ganglion.

Congenital delay of depolarization-recovery of ventricular myocardium is shown in the e.c.g. as prolongation of the Q–T interval. It is a rare inherited condition (Romano, Gemme and Pongiglione, 1963; Ward, 1964) which was first described in association with deafness (Jervell and Lange-Nielsen, 1957).

It can cause syncope or sudden death at any age, usually following physical exertion or strong emotions which may result in ventricular fibrillation. Surgery or anaesthesia may cause such an attack (Wig et al., 1979). We describe some preventive measures in the anaesthetic management.

CASE REPORT

A 27-yr-old female with a 5-year history of gynaecological complaints was referred for laparotomy. She had been admitted for operation in another hospital earlier in the year, but the procedure was abandoned after induction of anaesthesia because the patient developed ventricular fibrillation when pancuronium 1 mg was given i.v. to prevent muscle fasciculations following suxamethonium. Cardiac massage was applied externally and the rhythm reverted to normal spontaneously.

The patient had suffered attacks of syncope from the age of 7 yr usually associated with physical exertion. The symptoms were worst at the age of 21 yr when they occurred several times per week. The patient was diagnosed as suffering from epilepsy for many years, but when she was referred to the Cardiology Department at Uppsala aged 22 yr, an increased Q–T interval was discovered. Propranolol was prescribed but she had failed to comply because of intolerance to exercise and bradycardia. However, the syncopal attacks diminished in frequency and the last before the one reported above had occurred 5 years previously.

Two pregnancies and two laparotomies under general anaesthesia had been without complications. The patient's sister had suffered from attacks of syncope as a child and her mother, and her two children, had prolonged Q–T intervals without symptoms.

Physical examination, heart size and all laboratory results were normal and e.c.g. showed a Q–T interval of 0.56 s in all leads with normal T waves at a heart rate of 80 beat min^{-1} (normal value at this heart rate is 0.374 s). Metoprolol 200 mg orally was prescribed by the cardiologist for each of 2 days before operation. Premedication was with diazepam 15 mg orally 2 h before surgery and morphine 10 mg with hyoscine 0.4 mg i.m. 1 h before operation. Twenty minutes before induction of anaesthesia the left stellate ganglion was blocked percutaneously with 0.5% bupivacaine 8 ml, which produced obvious vasodilatation in the left arm, ipsilateral ptosis, but little difference in pupil size, probably because of the miotic effect of morphine. The patient was drowsy as a result of premedication and performance of the block had a minimal effect on heart rate. Propranolol 1 mg was given i.v. (parenteral metoprolol was unavailable) just before induction of anaesthesia, which was carried out with fentanyl 0.4 mg, thiopentone 200 mg and alcuronium 15 mg. Ventilation was controlled artificially via an endotracheal tube

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throughout the uneventful operation, e.c.g. was monitored at all times (precordial V5 lead) and a defibrillator was immediately available. After operation, two further injections of propranolol 1 mg i.v. were given at intervals of 8 h, and the e.c.g. monitored for 24 h.

Q–T intervals were normal shortly after induction of anaesthesia (fig. 1) but returned to pre-operative values in the course of the 2-h operation. The effect of the two injections of propranolol given during recovery on the Q–T interval was beneficial but small. However, the first measurement of the Q–T interval after induction of anaesthesia showed a remarkable relative shortening. Unfortunately, we could not obtain a paper record of the e.c.g. during the pre-induction period to measure Q–T intervals accurately and so we could not be certain its shortening had been caused by stellate ganglion block, beta blockade or anaesthetic agents used. To establish the therapeutic value of the stellate ganglion block in this patient, we decided to repeat it 4 days after operation, with the patient's co-operation, by percutaneous infiltration of the left ganglion with 5 ml of 1% lignocaine. Lead II of the e.c.g. was recorded at 5-min intervals and the Q–T intervals were briefly reduced to values within normal limits (figs 1, 2), in spite of minimal change in heart rate. A complete Horner's syndrome was apparent within 5 min of injection.

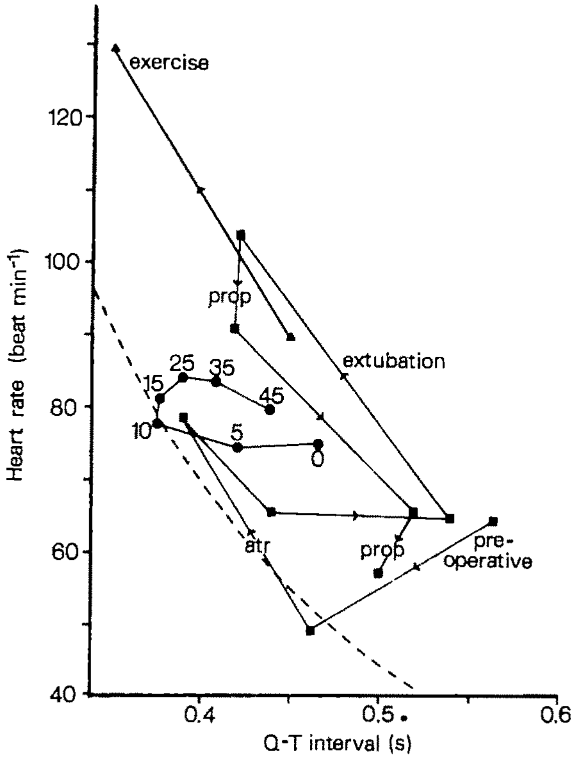

FIG. 1. Plots of heart rate against Q–T interval. ▲ = Response to exercise taken in 1974; ■ = values obtained at operation, arrows indicating direction of change; ● = response to left stellate ganglion block 4 days after operation (numbers are min from injection); atr = atropine 0.5 mg i.v.; prop = propranolol 1 mg i.v. Interrupted line represents upper limit of normal for women according to Bazett's equation: $Q\text{–}T/\sqrt{R\text{–}R} = 0.432$.

Atropine given during the operation also reduced the Q–T interval (fig. 1), with a corresponding increase in heart rate such that the change followed a line parallel to that defining the normal relationship between heart rate and Q–T interval (Bazett, 1920). Effects of arousal at extubation and of physical exercise were similar in nature to those of atropine. In figure 2, e.c.g. tracings are shown which correspond to some of the points plotted in figure 1, having superimposed the peaks of the first T waves for clarity. All the Q–T values plotted are averages of four consecutive measurements.

DISCUSSION

Schwartz, Periti and Malliani (1975) have reviewed more than 200 patients with this congenital syndrome; three-quarters of the untreated patients died, treatment with beta-blocking agents improved the survival rate considerably, and all those patients who had the left sympathetic supply to the heart surgically removed had survived.

The cause of Romano–Ward syndrome is unknown, but some evidence suggests that it is caused by imbalance of the sympathetic cardiac tone which is either exaggerated on the left or, more probably, depressed on the right (Schwartz, Periti and Malliani, 1975). This assymetry in tone delays repolarization of the ventricular myocardium, leading to an increase in its susceptibility to fibrillation (Han and Goel, 1972).

Percutaneous blockade of the right stellate ganglion was shown in one patient to increase the Q–T interval even further, whereas a left block reduced the interval to normal values; surgical denervation following this test suppressed the symptoms (Mors and MacDonald, 1971). Additional reports have confirmed the clinical success of this manoeuvre, even if in some instances the Q–T interval was not reduced to normal values (Yanagida, Kemi and Suwa, 1976; Callaghan, Nichols and Sweet, 1977).

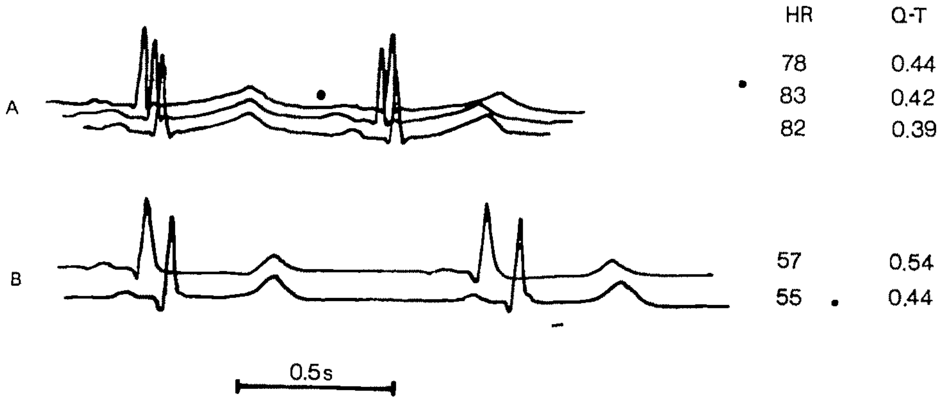

FIG. 2.A: E.c.g. tracings correspond to points 45, 35 and 15 of figure 1, obtained 4 days after operation (Lead II). B: Tracings (Lead V5) were obtained early at operation (bottom) and about 30 min after operation (top). T waves were superimposed in the first complex of all tracings for clarity of effects. The corresponding values of heart rate (HR) (beat min^{-1}) and Q–T interval (s) are given.

In the case presented here, the pre-operative left stellate ganglion block was successful in preventing complications, and was shown later to be effective in reducing the Q–T interval, indicating that this patient would possibly benefit from surgical sympathectomy, should her symptoms recur.

It was interesting to note the small effect of propranolol upon the Q–T interval in spite of its known therapeutic effectiveness (Milne, Camm and Ward, 1980).

Pancuronium is known to cause sympathomimetic effects on the heart and there is evidence in animal studies with clinical doses ($0.2\,\text{mg}\,\text{kg}^{-1}$) that this is a pre-synaptic indirect action by increasing the local release of noradrenaline (Domenech et al., 1976); this may be more apparent in a patient with an increased sympathetic tone caused by apprehension. This effect of pancuronium or its known parasympatholytic actions, or both, might have been precipitating factors of the ventricular fibrillation at previous induction of anaesthesia in our patient. Therefore, the use of agents such as pancuronium or atropine is probably best avoided in this condition.

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PROLONGATION DE L'INTERVALLE Q–T (SYNDROME DE ROMANO-WARD): CONTROLE DE L'ANESTHESIE

RESUME

Nous décrivons ici le contrôle de l'anesthésie d'un patient ayant un intervalle Q–T qui avait été compliqué par une fibrillation ventriculaire au moment de l'induction de l'anesthésie générale, lors d'une opération précédente. Cette complication a été évitée par une médication préopératoire efficace, grâce à du propranolol administré par voie intraveineuse et à un blocage du ganglion étoilé gauche.

VERLÄNGERUNG DES Q–T INTERVALLS (ROMANO-WARD-SYNDROM)—ANÄSTHESIEBEHANDLUNG

ZUSAMMENFASSUNG

Es wird die Anästhesiebehandlung bei einem Patienten mit verlängertem Q–T Intervall beschrieben, das durch Kammerflimmern bei der Einleitung der Narkose bei einer früheren Operation erschwert wurde. Diese Komplikation wurde durch entsprechende Prämedikation mit intravenös verabreichtem Propanolol und Blockade des linken Stellatumganglions verhindert.

PROLONGACION DEL INTERVALO Q–T (SINDROME ROMANO-WARD): GESTION DE LA ANESTESIA

SUMARIO

Se describe la gestión de la anestesia de un paciente que presentaba un prolongado intervalo Q–T, el cual se había complicado por la fibrilación ventricular durante la inducción de anestesia general en una operación anterior. Esta complicación se previno mediante una efectiva premedicación con propanolol intravenoso y el bloqueo del ganglio estrellado izquierdo.

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ELECTROMYOGRAPHIC MONITORING OF NEUROMUSCULAR BLOCK

H. S. Lam, N. M. Cass and K. C. Ng

SUMMARY

Neuromuscular blocking agents are widely used in anaesthesia, and a simple quantitative method of monitoring their effects is desirable. This paper describes a new instrument which has been developed for electromyographic monitoring of neuromuscular block by a non-invasive technique which is both reliable and easy to use. The median nerve is stimulated at the wrist and the electromyogram (e.m.g.) from a thenar muscle is detected, rectified and integrated electronically to produce a meter display of the assessment of block. The method is recommended for routine use.

Monitoring of neuromuscular blockade during anaesthesia is well established (Katz, 1970; Epstein and Epstein, 1975; Ali and Savarese, 1976; Katz and Katz, 1975) and can be assessed in the unconscious patient from stimulation of a motor nerve and measurement of either the force developed or the associated electromyogram (e.m.g.). The advantages of the evoked e.m.g. are that it presents fewer technical difficulties (Epstein and Epstein, 1973; Ali and Savarese, 1976) and electrical activity is considered to reflect events closer to the neuromuscular junction. In addition, the e.m.g. may be measured from muscles which are not accessible for mechanical recording.

Following the initial studies of Churchill-Davidson and Richardson (1952) various groups have used the e.m.g. to assess neuromuscular blockade. In some studies spontaneous electrical activity has been integrated with time and used as a measure of abdominal activity or ventilatory effort (Fink, 1960; Katz, Fink and Ngai, 1962). In others the peak amplitude of the evoked e.m.g. has been used to study the effects of drugs (De Jong and Freund, 1967; Ali, Utting and Gray, 1971; Epstein and Epstein, 1973; Katz, 1973). However, a simple system suitable for routine application without continuous attention is lacking. Two systems have been proposed in recent years. Epstein, Epstein and Lee (1973) reported the use of "time base expansion" by recording evoked e.m.g on FM magnetic tape which was subsequently played back at a slower speed. This technique has the obvious drawback that playback occurs after completion of all the recording, and the anaesthetist cannot make moment-to-moment clinical decisions. Lee and colleagues (1977) described an e.m.g. analyser which involved e.m.g. digitization, storage and playback with time expansion. The readout is not instantaneous, that is, the "quiet" period is used for analog waveform reconstruction on a chart recorder. Although this system permits continuous recording of the e.m.g., it is too elaborate in design for clinical monitoring where the actual waveform is of little merit in assessing blockade despite its high research value.

This paper presents a simple and non-invasive e.m.g. system which has been proven in over 300 patients at the Royal Children's Hospital, Melbourne. It is similar in principle to the method of Nightingale, Glass and Bachman (1966) who calculated the area enclosed by an evoked e.m.g. waveform and regarded it as an indication of the electrical activity resulting from indirect stimulation. Electronic rectification, integration and holding are used in the present development and the technique is recommended for routine practice.

METHODS

The monitor

The monitor unit is shown in figure 1: the controls provide adjustment of amplifier gain, stimulus amplitude and stimulus rate.

Electrical stimulus and e.m.g. pick-up

Stimulation and pick-up are effected by stick-on "Red Dot" silver/silver chloride e.c.g. electrodes

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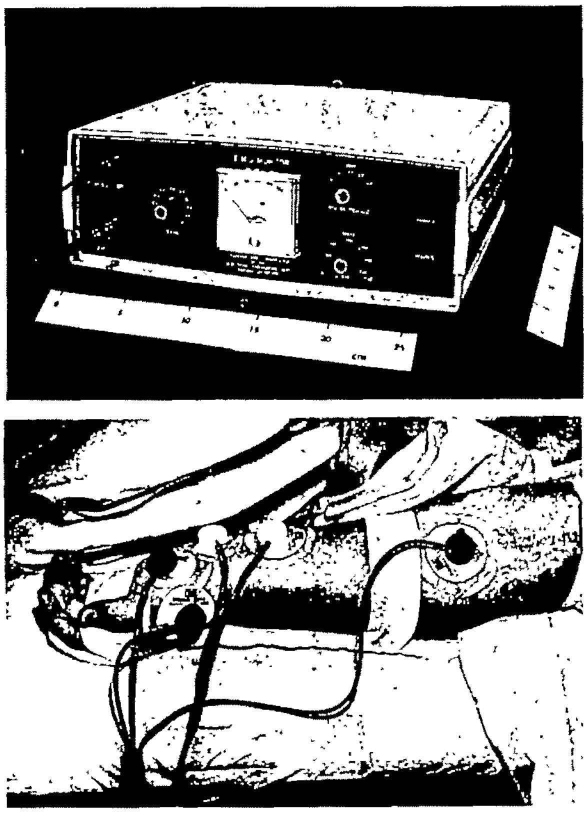

FIG. 1. The electromyographic monitor and placement of electrodes. Stimulus rates available on the unit are 0.1, 0.5, 1, 2 and 10 pulses per second. Stimulation of the median nerve is illustrated; the ulnar nerve may also be used.

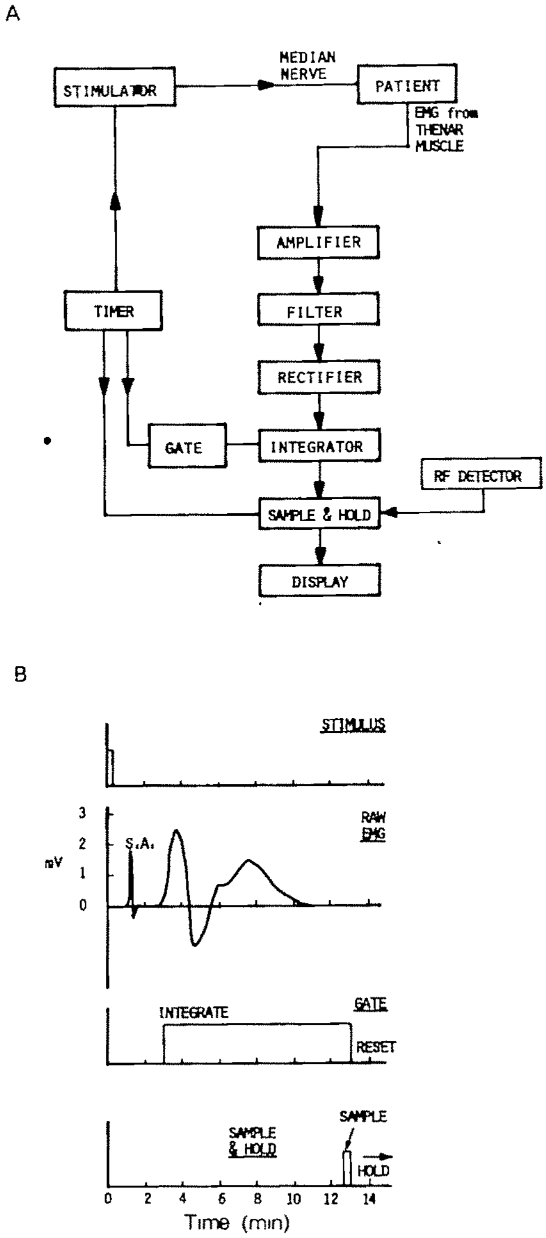

FIG. 2. A: Block diagram of the stimulating and e.m.g. processing unit. B: Time sequence of events and a typical trace of raw e.m.g. waveform with the stimulus artefact (S.A.).

(fig. 1). The median nerve is stimulated at the wrist with 0.1-ms pulses of amplitude up to 400 V. The compound e.m.g. is picked up from the thenar muscles, the electrodes being placed on the palmar aspect of the base of the thumb and the convexity of the skin over the dorsum of the second metacarpal. An indifferent electrode is placed at any point on the forearm or arm.

E.m.g. processing

The magnitude of the e.m.g. detected from normal muscle is in the range 0.5–5 mV. The signal is processed by an amplifier with high common-mode rejection (>90 dB, d.c. to 1 kHz, 1 kΩ imbalanced source), a filter (1–1000 Hz band-pass), a rectifier and an electronic integrator, giving a signal (in the range 0–10 V) proportional to the area enclosed by the rectified e.m.g. (fig. 2). The e.m.g. is gated, starting at 3 ms after the stimulus pulse is applied and lasting for 10 ms to exclude the stimulus artefact and electrical noise. Electronic integration occurs during this time and the output is sampled and held until the integrated e.m.g. resulting from the next stimulus is available. The final output is displayed as a value from 0 to 100 for easy assessment. A separate output terminal can be linked to a pen recorder. A timer initiates the stimulus pulse at fixed intervals and co-ordinates subsequent steps in the processing of the e.m.g.

Electrical interference in the e.m.g. is inevitable, especially when diathermy machines are used nearby. The sample-and-hold circuit was designed to detect high frequency interference from diathermy machines and prevent the acceptance of any further value until the interference has stopped. In this way spurious signals are rejected and the value displayed corresponds to the last unaffected stimulus sequence.

Electrical safety

The instrument is isolated from the electrical mains and there is no return path to ground from the patient.

Clinical application

Normal anaesthetic procedures need not be altered when the instrument is used. In our studies, all patients were premedicated with papaveretum 0.4 mg kg^{-1} and hyoscine 0.002 mg kg^{-1} s.c. 1 h before operation. Anaesthesia was induced with thiopentone 5.0 mg kg^{-1} i.v.

Electrodes were applied in the appropriate positions as described earlier. Since it was found that the output from the pick-up electrodes often decreased during 15–20 min following application, they were attached as soon as the patient reached the operating suite or at the pre-anaesthetic visit. Electrical connection to these electrodes was simplified by using leads with press-on clips. Stimulating pulses at the rate of 1 pulse per second (a reasonably fast rate to facilitate setting of the value in the absence of neuromuscular blockade) were applied to the wrist, the voltage being increased until a maximum twitch was observed, and then a further increase of 50 V was added to ensure supramaximal stimulation. The gain on the amplifier was adjusted until the display read 100. The rate of stimulation was then decreased to 1 pulse per 10 s to minimize fatigue. The unit was left to operate by itself for the duration of anaesthesia.

Following the injection of neuromuscular blocking drugs the decrease in the reading denoted the degree of blockade. Endotracheal intubation was performed with ease when there was 60–70% depression of the peripheral muscle e.m.g. Anaesthesia was maintained with 65–70% nitrous oxide in oxygen (any volatile or i.v. supplements may be used if qualitative results only are demanded).

A possible cause of noise in the recording system occurred if the hand was allowed to move, or if the electrodes moved in any way. To avoid these movements, the hand was loosely taped to a simple plastic splint.

RESULTS

Stable and noise-free recordings of integrated e.m.g. have been obtained in more than 300 patients. Figure 3A shows the integrated e.m.g. trace obtained from a young patient who had a single bolus dose of alcuronium 0.25 mg kg^{-1}. In figure 3B respiratory effort appears repeatedly when the integrated e.m.g. returned spontaneously to 20–25% control, so that additional doses of blocking drug were necessary.

The recording system can be set up in as little as 3 min by the anaesthetist or his assistant, and it requires no further involvement other than observation of the display.

The monitor has also been connected to a microprocessor unit for automatic drug infusion, with the integrated e.m.g. used as a feedback signal to regulate the administration of the neuromuscular blocking agent. This technique has been reported elsewhere (Brown et al., 1981).

DISCUSSION

The concept of integration of the e.m.g. is not new (Fink, 1960; Katz, Fink and Ngai, 1962; Nightingale, Glass and Bachman, 1966). However, the system described in this paper makes use of modern and standard electronic circuits to produce a compact unit containing the nerve stimulator, e.m.g. processor and output display. It is easy to operate and is able to provide an objective index to aid the anaesthetist in assessing the state of neuromuscular blockade (Katz and Katz, 1975). As stated earlier, the initial setting up takes less than 3 min and the system can be left self-running thereafter, without interference to the normal routine of the operating theatre. The whole unit can be placed on the anaesthetic machine for easy reference.

The technique recommended is totally non-invasive in that both the stimulation of the nerve and the detection of the e.m.g. are performed percutaneously. There is no risk of nerve injury, or of haematoma and infection which may occur with

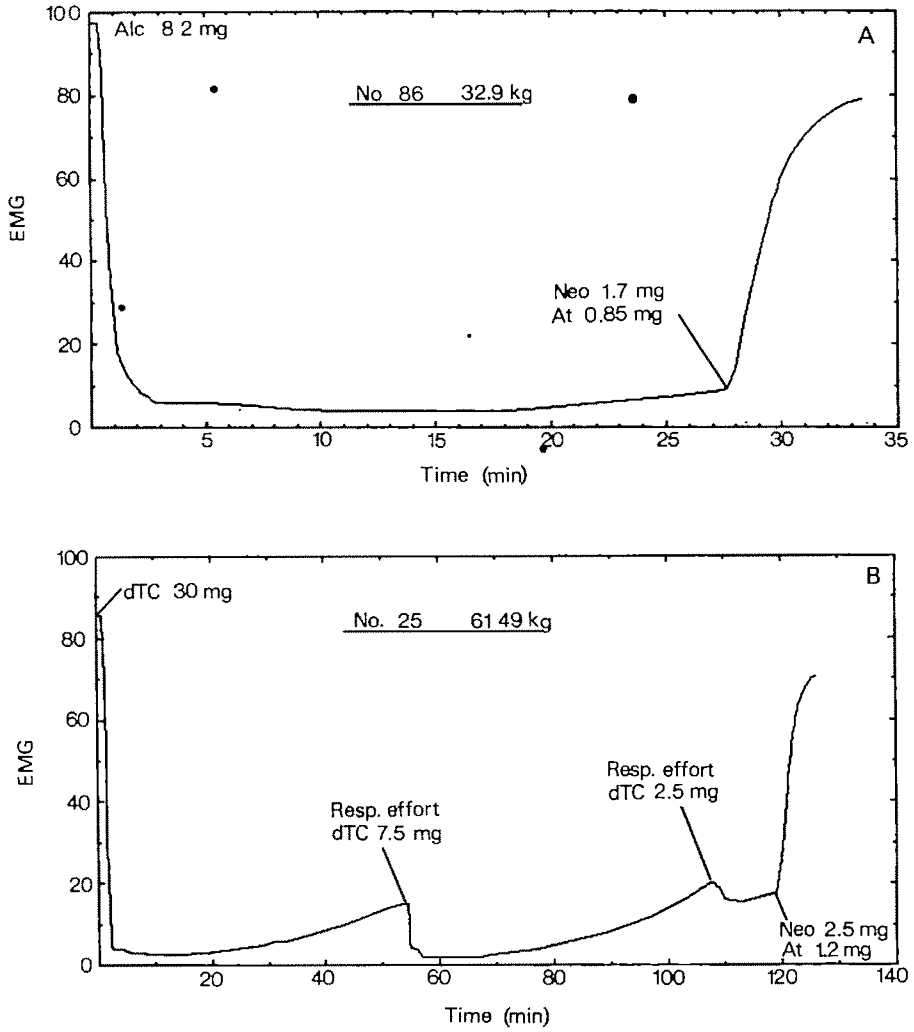

FIG. 3. Integrated e.m.g. recordings. The ordinate in arbitrary units showing e.m.g. value. A: Patient no. 86 (32.9 kg). Single bolus dose of alcuronium (Alc). The block was antagonized with neostigmine (Neo) and atropine (At). B: Patient no. 25 (61.4 kg). Multiple dosage of tubocurarine (dTC). Respiratory efforts noticeable at 10–25% level. Note the parallel slopes of the spontaneous recovery.

i.m. applications. Electrical burn has not occurred, in keeping with the very brief duration of the stimulus pulse (0.1 ms).

The relation between measured electrical activity and muscular force during indirect synchronous stimulation has been investigated and varying observations have been made (Ali, Utting and Gray, 1971; Epstein and Epstein, 1973; Katz, 1973; Lee et al., 1977; Lam, Morgan and Lampard, 1979; Shanks and Jarvis, 1980). Katz (1973) suggested that, where possible, both responses to nerve stimulation should be studied and if only one is obtained the choice will depend on the information desired. Shanks and Jarvis (1980) have recently produced data to confirm the use of integrated e.m.g. as an indication of clinical muscle paralysis, thereby supporting the use of our recording system.

The simplicity of design, ease of use and effectiveness of the monitor are the main reasons for recommending its adoption in routine evaluation of muscle paralysis in clinical practice.

The circuit diagram of the unit is shown in the Appendix (fig. 4). Technical details can be

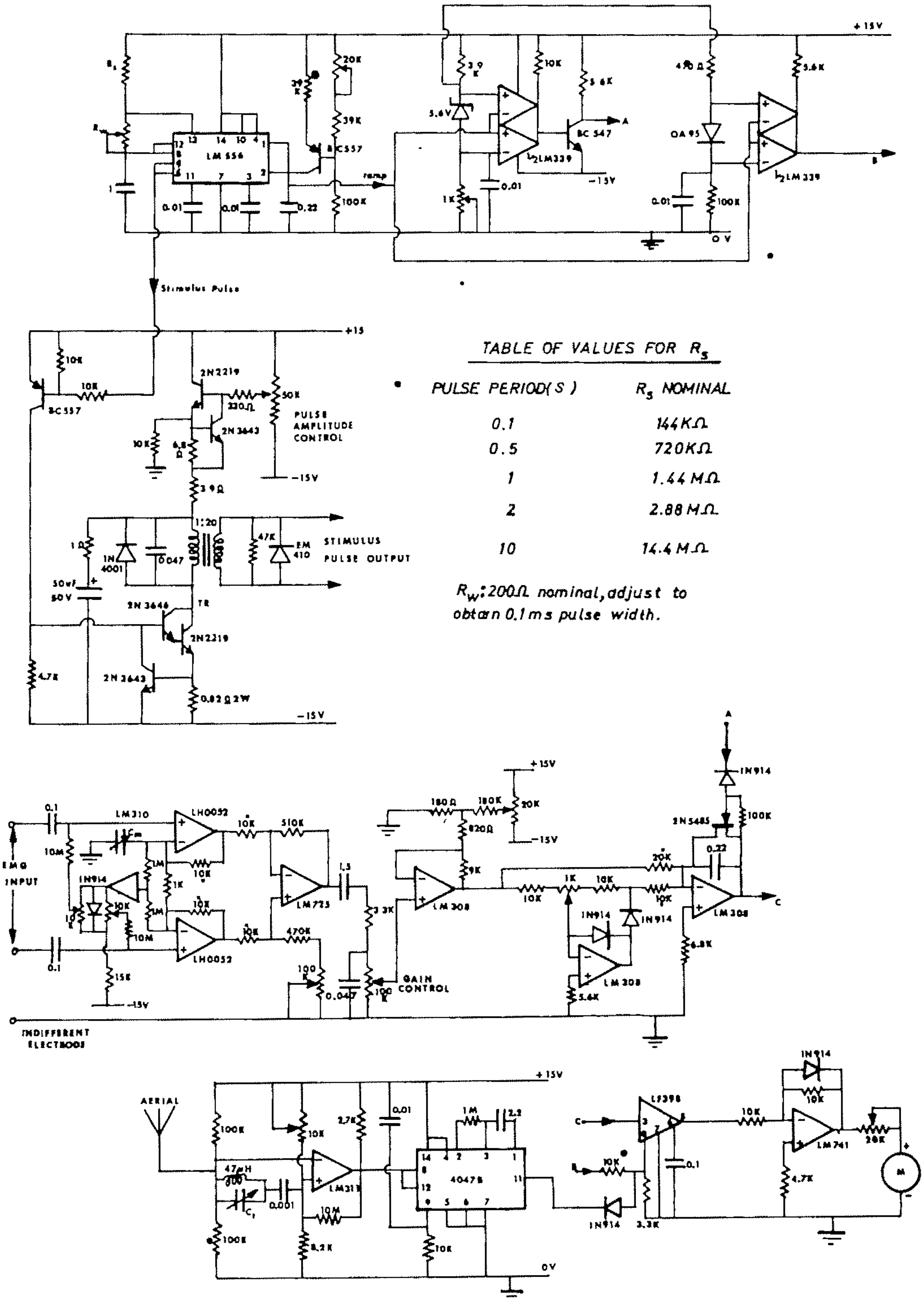

TABLE OF VALUES FOR R_S

PULSE PERIOD(S)	R_S NOMINAL
0.1	144KΩ
0.5	720KΩ
1	1.44MΩ
2	2.88MΩ
10	14.4MΩ

R_W: 200Ω nominal, adjust to obtain 0.1ms pulse width.

FIG. 4. Circuit diagram of the e.m.g. monitor.

obtained from the Department of Electrical Engineering, Monash University.

APPENDIX

CIRCUIT DIAGRAM OF THE E.M.G. MONITOR

Additional notes to circuit diagram (fig. 4)

(1) All resistors are 2% except those marked with crosses, which are 0.1%.
(2) R_w—200 Ω; adjust to give 0.1 ms pulse width.
(3) All capacitors are in units of μF.
(4) C_m—adjust for optimum a.c. common-mode rejection. Actual location may be from the negative input terminal of the other LH0052 to ground.
(5) C_T—select to suit frequency of diathermy used.
(6) TR—1 : 20 step-up transformer.
(7) M—1 mA moving coil meter.
(8) Decoupling and frequency compensation components are *not* shown. Refer to I.C. manufacturers' data sheets for these.
(9) Aerial is a 20-cm length of 22-gauge insulated wire.

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SURVEILLANCE ELECTROMYOGRAPHIQUE DU BLOCAGE NEUROMUSCULAIRE

RESUME

Les agents de blocage neuromusculaire sont largement utilisés en anesthésie et il est souhaitable d'avoir une méthode quantitative simple permettant de surveiller leurs effets. Cette communication donne une description d'un nouvel instrument qui a été mis au point pour surveiller à l'aide d'un électromyographe les blocages neuromusculaires, grâce à une technique non invasive qui est à la fois fiable et facile à employer. Lorsqu'on stimule le nerf médian au poignet, l'électromyogramme décèle, rectifie et intègre électroniquement un muscle adducteur et fléchisseur du pouce afin d'afficher sur le compteur l'évaluation du blocage. Cette méthode est recommandée pour les usages routiniers.

ELEKTROMYOGRAPHISCHE ÜBERWACHUNG DER NEUROMUSKULÄREN BLOCKADE

ZUSAMMENFASSUNG

Die Verwendung von neuromuskulären Blockierungsmitteln bei der Anästhesie ist sehr weit verbreitet und eine einfache quantitive Methode zur Überwachung ihrer Auswirkungen wäre wünschenswert. Diese Arbeit beschreibt ein neues Instrument, das zur elektromyographischen Überwachung der neuromuskulären Blockade von aussen entwickelt wurde und sowohl zuverlässig als auch einfach zu verwenden ist. Das Speichen-Ellennerv wird am Handgelenk gereizt und das EMG wird an einem Thenarmuskel entnommen, gleichgerichtet und elektronisch integriert, um eine Auswertung der Blockade anzuzeigen. Die Methode wird für routinemässige Verwendung empfohlen.

VIGILANCIA ELECTROMIOGRAFICA DEL BLOQUEO NEUROMUSCULAR

SUMARIO

Los agentes de bloqueo neuromuscular son muy usados en la anestesia y es deseable un método sencillo y cuantitativo para vigilar sus efectos. Este informe describe un nuevo instrumento que se ha perfeccionado para la vigilancia electromiográfica del bloqueo neuromuscular usando una técnica no invasora que es fiable y fácil de usar. El nervio mediano se estimula en la muñeca y se detecta el electromiograma procedente de un músculo tenar, y se rectifica e integra electrónicamente para producir una presentación en un medidor, que corresponde a la evaluatión del bloqueo. El método se recomienda para usarse en actividades rutinarias.

Br. J. Anaesth. (1981), 53, 1359

THE LEIDEN SCAVENGING SYSTEM: A SIMPLE AND VERSATILE APPARATUS TO CONTROL AIR POLLUTION IN OPERATING ROOMS

V. REJGER, A. G. L. BURM, J. SPIERDIJK AND H. STROKAP

SUMMARY

A scavenging system which can be attached to a variety of anaesthetic machines and ventilators is described. Gas venting can occur via a central vacuum system, a suitable injector, fan or pump, through the exhaust duct of an air-conditioning system, or by a passive system. The resistance and back pressures applied to the anaesthetic apparatus are negligible. Leakage tests showed that the collected gases and vapours were substantially removed by the scavenging device.

Disagreement exists about possible detrimental effects of chronic exposure to small concentrations of inhalation anaesthetics. There are, however, strong recommendations to reduce the degree of air pollution in operating rooms (Department of Health and Social Security, 1976; NIOSH, 1977). Air pollution can be controlled by an appropriate scavenging system (Bruce, 1973; Jørgensen, 1974; Parbrook and Monk, 1975; Lack, 1976; Asbury and Hancox, 1977; Mehta et al., 1977; Vaughan et al., 1977; Enderby, Booth and Churchill-Davidson, 1978).

The Leiden scavenging system has been developed as a versatile system. It is provided with interchangeable inlet connectors to enable connection to different anaesthetic machines and ventilators and interchangeable outlet connectors for different suction systems (vacuum system, injector, fan, pump or the exhaust duct of the air-conditioning system).

Criteria for a scavenging system

Like all other parts of the anaesthetic apparatus, scavenging systems must satisfy strict criteria to ensure patient safety. Such systems must be simple to operate and not require the attention of the anaesthetist when they are in use. Furthermore, a scavenging system must not exert any influence on the patient's breathing and circulation or disturb the efficiency of anaesthetic apparatus or ventilator. This means that criteria must be formulated for back pressures applied by the scavenging system on the patient system or the ventilator. Any sub-atmospheric pressures applied to the patient system must not of themselves be capable of opening valves in the circuit. In addition, the scavenging system must not offer excessive resistance to waste gas flow.

The limits set for the system under discussion are −50 Pa and +200 Pa, (≈ -0.5 to $+2\,\text{cm}\,H_2O$), the latter measured at a minute volume of $15\,\text{litre}\,\text{min}^{-1}$. A sub-atmospheric pressure of −50 Pa is compatible with most types of expiratory valves and ventilators. The proposed upper pressure limit results in practice in a modest increase in expiratory resistance and is compatible with nearly all ventilators.

The scavenging system

A schematic representation of the Leiden scavenging system (Hoekloos, Schiedam, The Netherlands) is given in figures 1 and 2. The system consists of a metal block with a device for attachment of a reservoir bag (2 litre), two inlets and a connector for the gas disposal system. Connector A is intended for connection to a high-pressure, low-flow source (vacuum system, injector, fan or pump). This connector is constructed such that, at a suction rate of 20–30 $\text{litre}\,\text{min}^{-1}$, up to 15 litre of waste gas can be removed per minute. The difference between the total suction rate and the amount of waste gas supplied is made up by the uptake of ambient air via four small holes (diam. 6 mm) in the connector (fig. 1) and two holes (diam. 10 mm) in the metal block (fig. 2). A restriction in the connector (diam. 9.3 mm) reduces the instantaneous flow rate of the waste gases emerging from the reservoir to a value less than the total suction rate. Thus, during the

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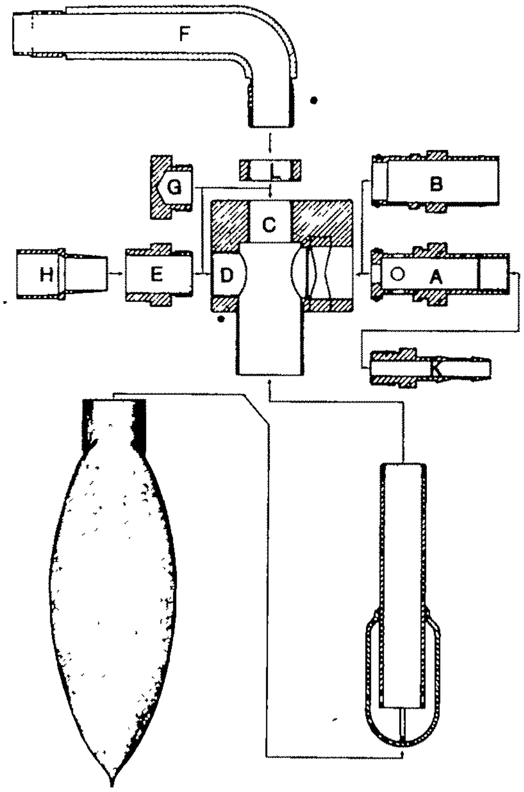

FIG. 1. The Leiden scavenging system: Exploded view. A = connector for high-pressure, low-flow suction unit such as a vacuum system; B = connector for attachment of tubing leading to the exhaust duct of the air-conditioning system or directly to the open air; C and D = inlets; E = 19-mm female conical inlet connector; F = inlet connector for direct attachment to the ventilator (connector for a Narkosespiromat 650 ventilator shown); G = blanking plug; H = 19-mm male conical connector for attachment of transfer tubing; K = vacuum spigot for 10-mm i.d. vacuum hose; L = fixation screw.

initial expiratory phase, when high flows of waste gases are supplied to the scavenging system, the excess amount is stored in the reservoir, which is completely emptied during the late expiratory phase and during the inspiratory phase, when no gases are vented. (Some ventilators actively vent waste gases during the initial inspiratory phase. The reservoir is then emptied during the late inspiratory and expiratory phases.) Connector A also prevents development of excessively high back pressures should the disposal system fail, since waste gases then escape via holes in the connector and in the metal block to room air.

Connector B is intended for connection to a wide-bore tube (i.d. 20 mm) which can be attached to a low-pressure venting system such as the exhaust grill of the air-conditioning system or led through the wall of the building to the outside air (passive system). Connectors A and B, as well as the inlet connectors E and F, are screwed to the metal block. The outlet connector cannot be interchanged with the inlet connectors. The metal block is provided with four screw-holes to attach a clamp making it possible to mount the system on an anaesthetic machine or ventilator equipped with a rail system. In this case, the connection between the scavenging system and the pollution control expiratory valve or the outlet of the machine can be made with 19-mm conical connectors (E and H, fig. 1) and light-weight plastic tubing (i.d. 20 mm). A 30-mm or 19-mm cone can be used to connect the tubing to the pollution control expiratory valve. It is often possible to connect the scavenging system directly to the ventilator outlet with special links such as F, figure 1, and thus avoid the use of tubes. The scavenging system is attached to a ventilator at inlet C.

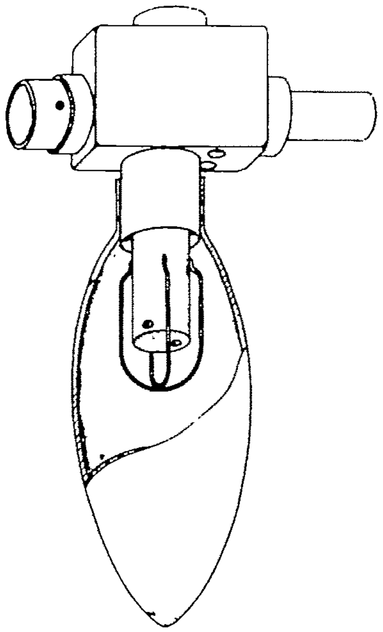

FIG. 2. The Leiden scavenging system assembled.

If only one of the inlets is required, the other can be closed with a blanking plug.

METHODS

Pressure fluctuations at the inlets were checked and a search was made for leaks before the scavenging system with connector A (high-vacuum low-flow system) was installed in the operating rooms. A 3-m vacuum hose was attached to connector A during these tests, as occurs in normal clinical practice. When no waste gas is supplied and the reservoir is empty, the sub-atmospheric pressure is maximal, equal at both inlets, and is determined by the suction rate and the diameter of the holes in the connector A and the metal block. To determine the maximum sub-atmospheric pressure that could occur, an inclined water manometer was attached at inlet C and inlet D was plugged. The suction rate was then varied using an adjustable fan. The positive pressures that developed at the inlets C and D while a continuous flow of air (15 or 30 litre min^{-1}) was introduced were also measured with an inclined water manometer. In addition, pressure fluctuations at the inlets were determined during intermittent supply of air. In these situations, the pressure always passed through a maximum while air was supplied (venting phase) and reached a minimum when the reservoir had been emptied. A preliminary study showed that, at a given minute volume (V_{min}) supplied to the system, the pressure depended mainly on the frequency at which the gases were supplied and on the instantaneous flow rate during the venting phase: the measured pressures increased with decreasing frequency (increasing tidal volume) and with increasing instantaneous flow rate.

The system was tested by connection to the outlet of an Engström 2000 ventilator which ventilated an artificial lung with air at a low frequency (10 cycles per min).

The Engström 2000 ventilator vents waste gases at a high and constant flow rate (2 litre s^{-1}) during the initial portion of the inspiratory phase, resulting in a square-wave flow pattern at the outlet. V_{min} was varied between 2.5 and 15 litre during the test. A hole was drilled in the wall of the connector which directly connected the scavenging system with the outlet of the ventilator and subsequently a tube was fitted into this hole so that it just reached to the inner surface of the wall. This tube was connected to a Statham P23 ID pressure transducer. The pressure signals were registered by a Siemens Mingograf 804 recorder. The maximum and minimum pressures were read from recorder tracings and recorded. Measurements were made at a total suction rate of 20.7 litre min^{-1} and also without suction, simulating a failed system. Checks were made for leaks using a similar arrangement with various conditions (V_{min} air = 1–15 litre; frequency = 10–20 per min; instantaneous flow rate = 0.25–2 litre s^{-1}). A small amount of smoke was added to the gas-stream, which was supplied as a square wave flow pattern, to demonstrate any leaks through the holes in the outlet connector A and the metal block. Total suction rate during this test was also 20.7 litre min^{-1}. A second test was made while a mixture of nitrous oxide (67%) and oxygen was supplied. The conditions were varied as described above. Nitrous oxide concentrations near the holes in the metal block were measured with a Miran 1A infra-red analyser calibrated for nitrous oxide.

The pressure at the inlet of the scavenging system, including outlet connector B but no tubing for connection to the exhaust grill of the air-conditioning or to a passive disposal system, was measured with an inclined water manometer while air was supplied at a constant flow rate of 1 litre s^{-1}.

RESULTS

Sub-atmospheric pressures measured at the inlet of the scavenging system with connector A and 3 m vacuum hose incorporated varied from −20 Pa at a suction rate of 20 litre min^{-1} to −50 Pa at a suction rate of 30 litre min^{-1}. The positive pressures measured at inlet C with continuous gas flows of 15 litre min^{-1} and 30 litre min^{-1} were 20 and 120 Pa respectively at a suction rate of 20.7 litre min^{-1} and 36 and 165 Pa when no suction was applied. The pressures measured at inlet D under the same conditions were slightly less. It is clear that the pressures measured at continuous flows differ from those measured at intermittent flows. Figure 3 shows the maximum pressures measured at inlet C. Minimum pressures varied between −20 Pa and +20 Pa depending on V_{min} and whether suction was applied or not. Figure 3 shows that, with a suction flow of 20.7 litre min^{-1}, pressures measured at inlet C were always within the proposed limits of −50 Pa and +200 Pa. At greater suction flows, smaller pressures will be measured and if no suction is applied, greater values occur. However, even in the latter case, the pressure exceeded 200 Pa only under conditions rarely encountered in anaesthetic practice. Pressures measured at inlet D differed somewhat from those at inlet C under

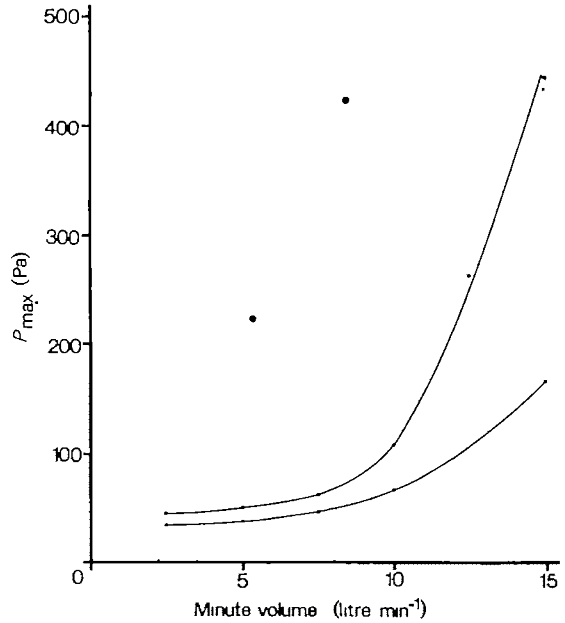

FIG. 3. Graphs indicating the maximum back pressures measured at inlet C of the high-vacuum low-flow scavenging system at different vented minute volumes during ventilation of an artificial lung with an Engström 2000 ventilator (frequency 10 cycles per min). Upper graph: no suction applied; lower graph: suction rate 20.7 litre min^{-1}.

the same conditions, but were also well within the proposed limits. As mentioned previously, the maximum pressures measured at a given V_{min} will be less if frequency is greater (smaller tidal volume) or instantaneous flow rate is less.

Leaks through the holes in connector A depend mainly on the amount of waste gas supplied per min and the instantaneous supply flow rate. If inlet C is used, leaks will occur only when the reservoir bag is completely filled. No leaks could be demonstrated at realistic combinations of frequency, tidal volume and instantaneous flow rate. If inlet D is used, leaks depend mainly on the instantaneous flow rate. At flow rates greater than 1 litre s^{-1}, small leaks were found. Therefore, inlet C should be used for attachment to a ventilator. It is clear that if the suction flow is greater than 20.7 litre min^{-1}, leaks will develop less rapidly. When considering the results of measurements made with intermittent flows, it should be emphasized that use was made of square-wave flow patterns. In practice, large flow rates are usually of very short duration and the positive pressures are correspondingly less.

The scavenging system with connector B incorporated has a very small resistance to gas flow. The pressures measured at inlet C and inlet D were 50 Pa and 15 Pa respectively at a continuous flow of 1 litre s^{-1} with no suction applied.

DISCUSSION

The scavenging system described in this paper was developed to permit attachment to most of the available types of anaesthetic machines and ventilators. A special connector makes it possible to connect the device to a high-vacuum low-flow suction system (suction flow 20–30 litre min^{-1}). Another connector can be used to connect the system to a passive disposal system or the exhaust duct of the air-conditioning system. With this arrangement, the function is primarily to reduce peak pressures that can develop if the released gases are led directly into the disposal tubing.

Choice of the most suitable method will often depend on the local situation and will be influenced by availability of a compressed air system, capacity of the vacuum system and location of the operating room. If an air-conditioning system is used, the negative pressure at the connection point must not exceed 50 Pa. For a passive system, the pressure at the terminal point is determined by the location and construction of the discharge end of the piping system, the wind velocity and direction and the presence of other buildings and obstructions in the vicinity (Department of Health and Sociel Security, 1976). The system described is effective in reducing the degree of air pollution in operating rooms. The nitrous oxide and halothane concentrations measured in our theatres in the "breathing zone" of the anaesthetist with a Miran 1A infra-red analyser and a personal sampling technique (Burm and Spierdijk, 1979), were reduced by 80–95% after installation of the scavenging system. The small degree of air pollution persisting after installation resulted mainly from leaks which are usually present in the anaesthetic apparatus and the high pressure gas supply system (Berner, 1978) and to a lesser degree from diffusion through rubber and plastic materials and through the holes in the outlet connector A of the scavenging system. Theoretically, the contribution of diffusion to operating room air pollution is negligible.

ACKNOWLEDGEMENTS

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LE SYSTEME D'EPURATION LEIDEN: APPAREIL SIMPLE ET POLYVALENT DE LUTTE CONTRE LA POLLUTION DE L'AIR DANS LES SALLES D'OPERATIONS

RESUME

L'auteur décrit un système d'épuration que l'on peut fixer à divers appareils d'anesthésie et aux ventilateurs. L'évacuation du gaz peut se faire par l'intermédiaire d'un système central à vide, d'un injecteur approprié, d'un ventilateur ou d'une pompe, par le conduit d'échappement d'un système de conditionnement de l'air ou par un système passif. La résistance et la contre-pression appliquées à l'appareil d'anesthésie sont négligeables. Les essais que l'on a fait pour déterminer s'il y avait des fuites ont fait ressortir que les vapeurs et gaz collectés étaient largement éliminés par le dispositif d'épuration.

DAS LEIDEN-SPÜLSYSTEM—EIN EINFACHES UND VIELSEITIG VERWENDBARES GERÄT ZUR BEKÄMPFUNG VON LUFTVERUNREINIGUNG IM OPERATIONSRAUM

ZUSAMMENFASSUNG

Es wird ein Spülsystem beschrieben, das an verschiedene Anästhesiegeräte und Ventilatoren angeschlossen werden kann. Ableitung des Gases kann über ein zentrales Vakuumsystem, einen passenden Injektor, Gebläse oder Pumpe, die Abluftleitung einer Klimaanlage oder durch ein passives System erfolgen. Der am Anästhesiegerät angebrachte Widerstand und Gegendruck sind geringfügig. Durchsickerungsversuche zeigten, dass die angesammelten Gase und Dämpfe im Wesentlichen durch das Spülgerät entfernt wurden.

SISTEMA LEIDEN DE BARRIDO: UN APARATO SENCILLO Y VERSATIL PARA CONTROLAR LA POLUCION DEL AIRE EN LOS TEATROS DE OPERACIONES

SUMARIO

Se describe un sistema de barrido que puede fijarse a una diversidad de máquinas y de ventiladores. La ventilación de gas puede efectuarse a través de un sistema central de vacío, de un inyector apropiado, de un ventilador o de una bomba, vía el conducto de salida de un sistema de aire acondicionado, o mediante un sistema pasivo. La presión de resistencia y la contrapresión aplicadas al aparato anestésico son despreciables. Las pruebas de fugas mostraron que los vapores y gases recogidos fueron substancialmente absorvidos por el dispositivo de barrido.

Br. J. Anaesth. (1981), 53, 1365

CORRESPONDENCE

POSTOPERATIVE EFFECTS OF METHYLPHENIDATE

Sir,—Drs Dodson and Fryer (1980) suggest that methylphenidate drug may be of value in increasing wakefulness, stimulating respiration and preventing shivering during the early postoperative period.

I believe that it is not only worthwhile but imperative to report briefly two unpleasant experiences after methylphenidate administration.

Patient 1. A 60-yr-old hypertensive female received general anaesthesia for breast biopsy followed by modified radical mastectomy. Before operation the arterial pressure was controlled with methyldopa. Anaesthesia was induced with thiopentone, pancuronium was administered to provide neuromuscular blockade and the trachea was intubated. Anaesthesia was maintained with nitrous oxide in oxygen, 0.2% halothane delivered from a Fluotec Mark II vaporizer and fentanyl 2μg/kg·body weight. During the surgical procedure systolic arterial pressure fluctuated between 17.3kPa and 19.5kPa. At the end of surgery the neuromuscular blockade was antagonized with atropine and neostigmine. The patient responded to verbal commands and systolic pressure was found to be 21.28kPa. A few minutes later, when she started shivering, methylphenidate 20mg was administered i.v. slowly. Five minutes later the patient became unconscious and apnoeic. It was thought that she had a cardiac arrest, but peripheral pulses were palpable and the systolic pressure was increased to 37.2kPa. This abrupt increase in pressure obviously caused cerebral oedema, or possibly a cerebral episode. The lungs were ventilated manually with oxygen and air and frusemide 80mg and prednisolone 50mg i.v. were given. The patient responded favourably and recovered completely. Urine output was about 1500ml and systolic pressure decreased to 23.9kPa.

Patient 2. A 42-yr-old female received general anaesthesia for excision of a breast lump. Before operation arterial pressure and e.c.g. were normal. During the early period after operation and while the patient was recovering smoothly with systolic pressure 17.29kPa, methylphenidate 20mg was administered i.v. slowly because the patient started shivering. Within the next few minutes she became unconscious and apnoeic. Systolic arterial pressure was found to be 29.26kPa. Frusemide and prednisolone were given i.v. with artificial ventilation of the lungs. The response was satisfactory and recovery uneventful.

Postoperative shivering is unpleasant for the patient and undesirable for the anaesthetist. It is known that oxygen consumption may be doubled. In both these cases methylphenidate was administered to stop and not to prevent shivering.

After these experiences with methylphenidate, we keep the patients as warm as possible and give oxygen via a Ventimask. We found that methylphenidate 10mg given i.v. slowly is quite sufficient to stop shivering and does not affect the cardiovascular system.

Drs Dodson and Fryer did not exclude or at least did not mention hypertension, tachycardia (of whatever cause) and cardiovascular disease. Their study included patients of 70 years. Did the authors correlate the age with the restlessness observed in the four patients after the methylphenidate administration? They claim increased respiratory stimulation in the early period after operation. At that time I would expect an increase in c.n.s. oxygen consumption and an increased oxygen consumption by the heart (increase in arterial pressure and in heart rate, increased work).

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Sir,—Only moderate increases in arterial pressure and heart rate had been reported after clinical use of methylphenidate, and we observed such increases. Table III of our article reports a mean systolic arterial pressure increase of 2.14kPa after halothane–methylphenidate, and a mean heart rate increase of 22beat min^{-1}. The increases were smaller after fentanyl–methylphenidate, and the largest increase in systolic arterial pressure was 6.8kPa.

Potentiation of the inotropic effect of noradrenaline on the dog's heart by methylphenidate has been reported by Maxwell and others (1961). Increased catecholamine secretion occurs during shivering, and arterial pressure also increases; Borotoluzzi and others (1963) report a pressure of 30.1kPa during shivering and before administration of methylphenidate, with a decrease in arterial pressure after the administration of the drug. Both patients of Dr Fassoulaki were shivering when the methylphenidate was given when increased sympathetic activity must have been present. The importance of such activity in causing adverse reactions to methylphenidate is supported by Brichard and Johnstone (1970). Ventricular extrasystoles or tachycardia occurred in five patients with a mild respiratory acidosis, and this could be treated or prevented by oxprenolol.

Methylphenidate may increase myocardial and c.n.s. oxygen consumption, but we suggest that this is probably less than the known large increase in muscle oxygen consumption which accompanies shivering. Although the administration of oxygen and warming are useful measures in the management of shivering, there may be occasions when the use of methylphenidate is considered. We agree with Dr Fassoulaki that the smallest effective dose should be used, and her two reports suggest that particular care should be taken in administering methylphenidate to hypertensive patients, especially when increased sympathetic activity is present, for example, when shivering is established.

We did not find any correlation between age of patient and restlessness. We did not claim increased respiratory stimulation, but that "there was significantly less deterioration (in respiratory function) when methylphenidate was given with halothane."

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ATRACURIUM IN ANAESTHETIZED MAN

Sir,—I read with great interest the paper by Drs Payne and Hughes (1981) on the evaluation of atracurium in anaesthetized man. The rapid onset and relatively short duration of action and the absence of circulatory side-effects of atracurium are equally impressive. I am concerned, however, about the method of administration of atropine and neostigmine used for the antagonism of the residual atracurium block. It appears from figure 3 of their paper that atropine 1.2 mg had been administered 2–3 min before the injection of neostigmine. It has been reported (Rosner, Kepes and Foldes, 1971) that, when atropine 12 μg kg^{-1} (0.84 mg per 70 kg^{-1}) was injected i.v., the mean heart rate in a group of 10 patients increased from 72.2 ± 3.5 (SEM) to 101.2 ± 49 in 2 min. When the same dose of atropine was injected with neostigmine 40 μg kg^{-1} (2.8 mg per 70 kg^{-1}), up until 3 min, there was a moderate increase of the mean heart rate followed by moderate bradycardia. This sequence of events results from the fact that atropine reaches muscarinic receptor sites in the heart more rapidly than does neostigmine. What were the heart rates of the patients just before and 2 min after the i.v. injection of atropine 1.2 mg kg^{-1}?

One of the main advantages attributed to atracurium over other neuromuscular blocking agents in clinical use is that it does not increase the heart rate during induction of anaesthesia. If this is so what is the rationale of using atropine in a manner that will result in tachycardia at the end of anaesthesia?

I believe that when a short acting neuromuscular blocking agent such as atracurium is used judiciously, less than 2.5 mg of neostigmine (1.2–1.5 mg) will produce satisfactory antagonism of the residual neuromuscular block. We have had no opportunity for the clinical use of atracurium, but our experience with Org NC 45, another short-lasting neuromuscular blocking agent, confirms the validity of this assumption.

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Sir,—First, we find it curious that Dr Foldes should be concerned about our method of administering atropine and neostigmine. In the United Kingdom it is common and in our view sound practice to delay the injection of neostigmine until the heart rate has increased in response to the atropine. The practice developed following independent communications by MacIntosh (1949) and Clutton-Brock (1949) in which sudden death was reported to have occurred in two critically ill patients immediately after the simultaneous injection of atropine and neostigmine. At that time Bain and Broadbent (1949) pointed out that, under some circumstances, atropine could potentiate the cardiac slowing property of neostigmine, and that in their opinion the simultaneous injection of both drugs was contraindicated. Our own experience and the many anecdotal accounts of severe bradycardia and hypotension after atropine and neostigmine have been given together reinforce this advice and we see no reason to disagree with the interpretation of Bain and Broadbent (1949). It may well be true that Dr Foldes and his colleagues (Rosner, Kepes and Foldes, 1971) were unable to demonstrate such a relation in their series of 50 patients, but presumably these patients were not critically ill and had normal circulatory systems. In our patients the heart rate increased from a mean value of 56.8 ± 4.9 (SEM) immediately before the injection of atropine to 78.1 ± 4.7 1 min later.

Again, Dr Foldes claims that one of the main advantages attributed to atracurium over other neuromuscular blocking agents in clinical use is that it does not increase the heart rate during induction of anaesthesia. We have made no such claim; we merely drew attention to the cardiovascular stability after injection of the drug as evidence that it did not release histamine (Payne and Hughes, 1981). Furthermore, we do not regard a heart rate of less than 80 beat min^{-1} at the end of anaesthesia as evidence of tachycardia; but even if it were so, it scarcely justifies an alteration in our practice.

Finally, we believe that when a short-acting neuromuscular blocking agent such as atracurium is used judiciously there should be no need to antagonize its action with neostigmine, which carries its own risks (Payne, Hughes and Al-Azawi, 1980).

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LEAK FROM AN OXYGEN FLOWMETER

Sir,—The report of Powell (1981) is yet another example of the reduction in delivered oxygen percentage to be expected from an oxygen flowmeter on the left-hand side of a flowmeter manifold when a leak occurs anywhere in the manifold. Eger and colleagues (1964) first drew attention to the importance of locating the oxygen flowmeter *on the right* next to the flowmeter manifold outlet to prevent such a loss of oxygen. Bishop, Levick and Hodgson (1967) reported two accidents caused by this "fundamental fault in the design of the Boyle machine"; Katz (1968) and Liew and Ganendran (1973) reported similar accidents. In 1975, a report by Gupta and Varshneya, of a death attributable to the escape of oxygen through the washer intended to seal the top of a downstream flowmeter in a Boyle-type machine, drew further comment (Muliyil, 1976; Rendell-Baker, 1976; Varshney, 1976) through correspondence.

There are two ways to eliminate this hazard. The simplest, mechanically, in the Boyle-type machine is to relocate the oxygen flowmeter to the right-hand side of the manifold. This could be performed in the hospital by the manufacturer's serviceman, thus requiring that the apparatus be out of service for a minimum time. This solution will require a re-education programme for anaesthetists similar to that mounted when the colours of gas cylinders were changed in the 1950's.

The other more difficult and expensive solution would be to fit an internal conduit in the top of the flowmeter manifold to conduct the oxygen directly to the outlet of the manifold as described by Katz (1969). This would require the return of the flowmeter manifold to the manufacturer to be rebuilt or the purchase of a new flowmeter manifold incorporating the oxygen conduit.

With present hospital budget problems the first solution—"oxygen on the right"—has both financial and mechanical arguments in its favour as a safety measure.

After all, Henry Ford managed to persuade our fathers to change from a hand throttle on the steering wheel on his Model T to a foot-accelerator on the right with his Model A . . . would it really be so difficult to change to "oxygen to the right?"

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HUNTINGTON'S CHOREA

Sir,—Further to the article by Farina and Rauscher (1977), we report the successful anaesthetic management of two patients with Huntington's chorea.

Two brothers presented with chronic left lower lobe consolidation and pleural effusion. Left pleural decortication was the surgical treatment indicated. The elder (aged 25 yr) had frank manifestations of Huntington's chorea (dysarthria, dementia, ataxia, and choreiform movements), while the younger (aged 19 yr) had early signs of the disease (ataxia, and occasional choreiform movements).

The patients received papaveretum and hyoscine before operation. Anaesthesia was induced with thiopentone. Suxamethonium facilitated bronchoscopy and tracheal intubation with a Robertshaw double-lumen tube. Further muscle relaxation was provided by pancuronium and analgesia by fentanyl and nitrous oxide. Both operations were uneventful. Neuromuscular blockade was antagonized with neostigmine and atropine.

Davies (1966) suggested that patients with Huntington's chorea might be unduly sensitive to barbiturates. This problem did not arise with our patients.

Gualandi and Bonfanti (1968) postulated that prolonged apnoea, as a result of abnormal plasma cholinesterase activity, may follow the use of depolarizing muscle relaxants. We measured plasma cholinesterasec concentrations before operation in both patients:

Plasma cholinesterase: 0.73 and 0.61 iu ml^{-1} (normal values 0.6–1.4 iu ml^{-1}
Dibucaine numbers: 79 and 83
Fluoride numbers: 69 and 57
Probable genotype for both patients: $E_1^UE_1^U$

We agree with the suggestion of Farina and Rauscher that the anaesthetic requirements of patients with Huntington's chorea can be provided by a nitrous oxide–narcotic combination, and successful management of myoneural blockade by pancuronium.

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ADVERSE REACTIONS TO I.V. ANAESTHETICS

In response to enquiries regarding the number of patients studied by Drs Beamish and Brown (*Br. J. Anaesth.*, 53, 55), we are pleased to publish the following letter from Dr Brown:

The number of administrations of each induction agent—from which we calculated frequencies of reactions—was the total number of administrations of the anaesthetic including those in which other drugs, including relaxants, were used.

Our sentence "Patients who received muscle relaxants were not included in this study" is misleading and is the source of confusion. The sentence referred to the design of the study in which we intended to include only those reactions which were clearly the result of an induction agent and to exclude any *reactions* in which a relaxant had been used at induction. This was to avoid reactions where it was not absolutely clear whether the induction agent or the relaxant had caused the problem. In the end we did not have to exclude any reactions on this basis, which is perhaps a matter for comment.

We have therefore calculated the minimum frequency of reactions for each drug. We believe this is the best way to present these figures.

David T. Brown
Edinburgh

SEDATION FOR UPPER GASTROINTESTINAL ENDOSCOPY

Sir,—In my practice, which differs from that of Dr Nimmo (Douglas et al., 1980; Nimmo, 1981), the patients need guaranteed and immediate sedation; I doubt if temazepam can provide this (Harris, 1981).

After more than 12 000 gastroscopies with 30–40 patients per session, the "turn around time" for outpatients averages 5 min comprising: about 1 min for injection, 1–2 min for gastroscopy, and about 2 min to remove the patient from the table and position the next one. Some patients, particularly those bleeding briskly or when multiple biopsies are needed, take much longer to examine.

I use pre-mixed diazepam and hyoscine (Buscopan) 20 mg each. Most fit patients receive the full dose in less than 30 s without titration (which would delay the procedure); the elderly or frail receive less. In almost all patients adequate and rapid sedation ensues; the vast majority cannot recall the examination, which is a major reason why most are willing to have the procedure repeated. None has had respiratory problems.

More patients given temazepam could recall the procedure; this suggests the sedation was less than with diazepam despite a 10-min interval between the injection and endoscopy, by which time the peak sedative effect would have passed in many. In my experience inadequate sedation prolongs the examination and makes patients reluctant to re-attend.

For the few patients with recurrent thrombophlebitis from i.v. diazepam, I will certainly use oral temazepam. But in my peculiar type of endoscopy practice, there is as yet no substitute for i.v. diazepam.

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P.V.C. CUFFS AND LIGNOCAINE-BASE AEROSOL

Sir,—Horatz (1977) observed that an aerosol of lignocaine base can cause pin-holes in the inflated cuffs of endotracheal tubes, and suggested that lignocaine-base aerosol should not be used when it could be sprayed on p.v.c. cuffs.

We have noted that a droplet of the aerosol on a p.v.c. cuff causes: (1) no effect on its inflation; (2) occurrence of a pin-hole after a short interval; (3) the raising of a blister on the inflated cuff or, (4) sudden rupture of the cuff.

These different effects depend on the size of the droplet, whether it spreads or is localized, and the extent of stretch of the cuff membrane.

The explanation which we suggest is that the aerosol contains a swelling agent for the cuff. The different effects are explicable in terms of the rate of its diffusion and the changes it causes on the mechanical properties of the cuff membrane. Swelling agents soften a polymer and decrease its tensile strength. If it is in insufficient localized quantity, it merely causes a marginal softening of the cuff membrane and an insignificant increase in cuff volume (effect (1) above). If the tensile strength in a small area is reduced below the tension in the membrane at that point, a micro-rupture occurs (pin-hole formation). If a larger area is softened, the pressure uniformly exerted on the inside of the membrane causes the softer region to stretch further and so form a blister. Finally, if a substantial amount of swelling agent is rapidly absorbed in a larger area, a tear occurs.

We made an aerosol with the same propellants containing 10% di-octyl-phthalate, a typical plasticizer for p.v.c. This aerosol produced all the above effects.

To confirm that Xylocaine Spray contained a swelling agent, pieces of cuff were immersed for 1 h in the pressurized liquid. After leaving in air for the propellants to evaporate, the cuff material increased in weight by between 10 and 15%.

The fluorocarbon propellants themselves did not evince any swelling action nor adversely affect an inflated cuff. Lignocaine-base is otherwise the only ingredient in significant quantity and appears to be the causative agent. This is not surprising from its dissolution in a wide range of organic materials up to the polarity of methanol—bracketing the polarity of p.v.c. As further confirmation, lignocaine-base crystals placed on an inflated cuff were absorbed into it and after 2–5 h could cause pin-holes and blisters. However, lignocaine hydrochloride (the salt) in solution or in crystal form had no effect on p.v.c. cuffs. Hence, as confirmed experimentally, gels or salves of the salt have no adverse effect on inflated p.v.c. cuffs. This correlates with the insolubility of the salt in p.v.c. and in organic materials including cyclohexane with a solubility parameter of 11.4, but in ethanol of 12.7, whereas p.v.c. has a solubility parameter of 9.5.

Astra Pharmaceuticals Ltd inform us that Xylocaine Spray is not recommended when it may contact p.v.c. cuffs. Xylocaine 4% topical and 2% gel—which contain the salt and not the base—are recommended. The above findings are in harmony with these recommendations.

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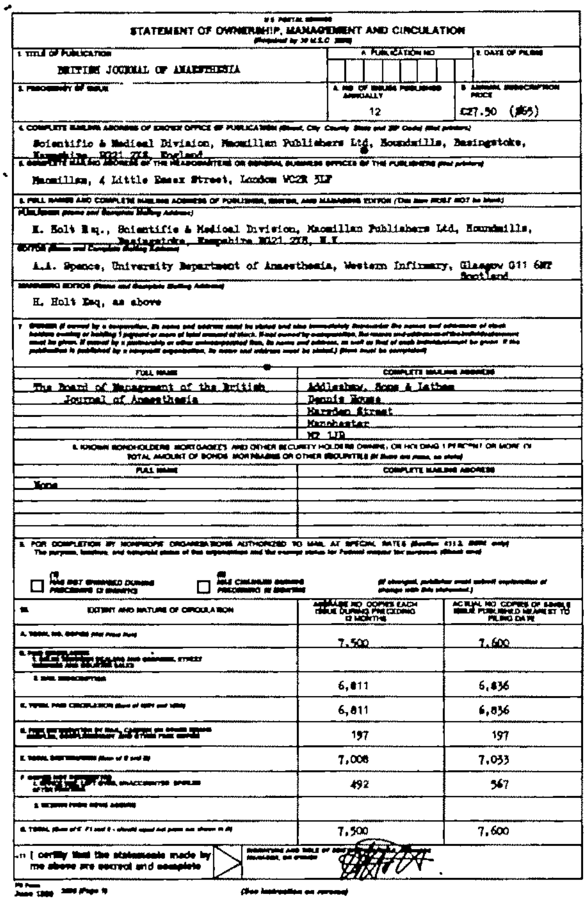

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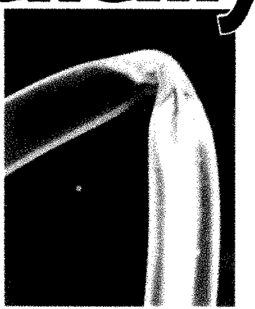
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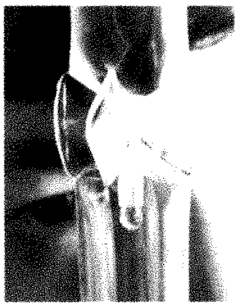
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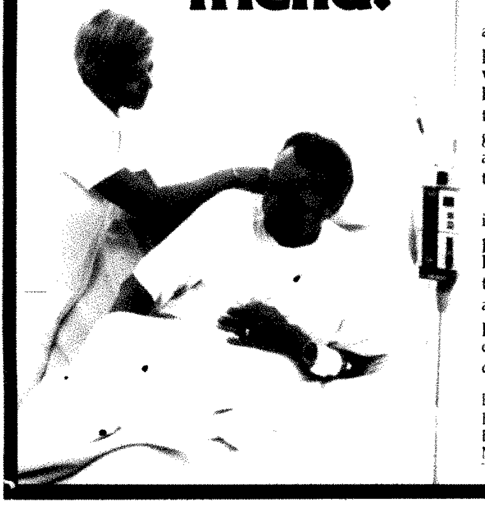

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